FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE

January 8, 2009

7:45 a.m.

Hilton Washington, DC/Rockville
Rockville, Maryland

C O N T E N T S

C O N T E N T S (Continued)

P A R T I C I P A N T S

Larry B. Goldstein, M.D., Acting Chair
Diem Kieu H. Ngo, Designated Federal Official

PERIPHERAL AND CENTRAL NERVOUS SYSTEM (PCNS)
DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Larry B. Goldstein, M.D., (Acting Chair)
Lily K.F. Jung, M.D., M.M.M. (Consumer Rep)
Ying Lu, Ph.D.
Matthew Rizzo, M.D.

TEMPORARY MEMBERS (Voting)

Marshall S. Balish, M.D.
Harry T. Chugani, M.D.
Stephanie Y. Crawford, Ph.D., MPH
Richard L. Gorman, M.D.
Richard R. Heckert, M.D.
Deborah G. Hirtz, M.D.
Jacqueline S. Gardner, Ph.D.
Frances E. Jensen, M.D.
Karl D. Kieburtz, M.D.
Eli Mizrahi, M.D.
Lewis S. Nelson, M.D.
Michael X. Repka, M.D.
Wayne R. Snodgrass, M.D., Ph.D.
Gerald van Belle, Ph.D.
Marielos L. Vega, B.S.N., R.N.
Constance E. West, M.D.

PERIPHERAL AND CENTRAL NERVOUS SYSTEM (PCNS)
DRUGS ADVISORY COMMITTEE MEMBER (Non-voting)

Roy E. Twyman, M.D. (Industry Rep)

Michael C. Bartenhagen (Patient Rep)

DRUG SAFETY AND RISK MANAGEMENT (DSaRM)
ADVISORY COMMITTEE MEMBER (Voting)

Judith M. Kramer, M.D., M.S.
Timothy S. Lesar, Pharm.D.

P A R T I C I P A N T S (Continued)

PEDIATRIC ADVISORY COMMITTEE MEMBER (Voting)

Leon Dure, M.D.

RISK COMMUNICATION ADVISORY COMMITTEE (RCAC) MEMBER (Voting)

Betsy L. Sleath, Ph.D.

FDA PARTICIPANTS (Non-Voting)

Robert Temple, M.D.
Russell G. Katz, M.D.
Wiley Chambers, M.D.
Sheridan, M.D.
Ronald Farkas, M.D., Ph.D.

P R O C E E D I N G S

Call to Order

DR. GOLDSTEIN: Good morning, everyone. Welcome to Day 2. We have much the same committee that was here yesterday. Before we begin, I need to go through some basic ground rules.

For topics, such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal at today's meeting is that it will be a fair, open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government and the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, the

FDA will refrain from discussing the details of the meeting with the media until its conclusion. A press conference will be held in the Washingtonian Room immediately following the meeting today. Also, the committee is reminded to please refrain from discussing the meeting topic during the breaks of lunch. Thank you.

As I said, the committee is the same as it was yesterday. My name is Larry Goldstein. I am the acting chair of the committee. We have two people who weren't here yesterday that I would just like to introduce themselves.

DR. REPKA: I am Michael Repka, from Johns Hopkins in Baltimore, and I am an ophthalmologist.

DR. GOLDSTEIN: And Dr. Kieburtz?

DR. KIEBURTZ: I am Karl Kieburtz. I am a neurologist in Rochester, New York.

DR. GOLDSTEIN: Very good. Next I think is Dr. Ngo.

Conflict of Interest Statement

DR. NGO: Before we start, would everyone please silence their cell phones and pagers, if you have not already done so? Also, Dr. Vega lost her flash drive in the business center last night. So, if anyone picked it up, it

has her name on it, please return it to her.

The Food and Drug Administration is convening today's meeting of the Peripheral and Central Nervous System Drugs Advisory Committees under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting and non-voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetics Act is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting and non-voting members of this committees are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial

conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting and non-voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for the purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts/ grants/CRADAs, teaching/speaking/writing, patents and royalties, and primary employment.

Today's agenda involves new drug application NDA 22-006, vigabatrin, sponsored by Ovation Pharmaceuticals, for the proposed indication of treatment of infantile spasms. This is a particular matters meeting during which

specific matters related to vigabatrin will be discussed.

We would like to disclose that Dr. Michael Rogawski is recused from participating in today's meeting. With respect to FDA's invited industry representative, we would like to disclose that Dr. Roy Twyman is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Twyman's role at this meeting is to represent industry in general and not any particular company. Dr. Twyman is employed by Johnson & Johnson.

We would like to remind members and temporary voting and non-voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firms at issue. Thank you.

DR. GOLDSTEIN: Thank you. Dr. Katz?

DR. KATZ: Good morning. I know I said yesterday

morning that I wouldn't be speaking today but I have been informed that I have one particular task, a somewhat bitter-sweet task to perform so I want to do that now.

As most of you know, our advisers serve on the committee for terms of either three or four years. If any of you are new to this process and were here yesterday you know how much work it is to be an advisory committee member. There is a tremendous amount of preparation beforehand; a lot of thinking goes into it; and then a great deal of work goes into performance at the meeting itself.

We have numerous meetings. It is a tremendous amount of work. Advisory committee members, for all intents and purposes, volunteer their time to us and, more importantly, to the people of the United States. We take this role very, very seriously and we are tremendously appreciative of the service that our advisory committee members give, again, to us and to the country.

So, as I say, I have the bitter-sweet task of announcing that several of our members who are here today are rotating off the committee. Their tenure is over I guess at the end of this month. So, we want to give them a plaque. Advisory committee members get a plaque. This is

in lieu of money basically.

The first plaque-Band, of course, they are all the same except for the namesB-is for Dr. Rizzo, of the University of Iowa, who has given a tremendous amount of time to the committee.

Let me just read it quickly: The Advisory Committee Service Award presented to Matthew Rizzo, M.D. in recognition of distinguished service to the people of the United States of America. I think that is an accurate description. So, Dr. Rizzo, if you could come up and take the award?

[Applause]

DR. RIZZO: Thanks very much.

DR. KATZ: Thanks very much. The next award is to Dr. Lily Jung, who also has been on since September of '05. Dr. Jung actually wore two hats really during her time here. She is the consumer representative but is also a neurologist so she has brought particular expertise in several different areas. So, if I could bring her up?

[Applause]

DR. KATZ: Thank you. The next award is actually a year late. That happens. This is an award for Dr. Karl

Kieburtz, from the University of Rochester. He rotated off the committee I think last year and is back as sort of a special government employee to help us with this issue today. Karl was chair of the committee and did a great job, and being chair is a difficult job sometimes but Karl was terrific. So, thanks very much.

[Applause]

DR. KATZ: Last, Dr. Larry Goldstein is rotating off. Dr. Goldstein has served as acting chair for the last several meetings. That is a thankless task and he has done a tremendous job, and we will see how he does today in his swan song. Dr. Goldstein's plaque is not here yet but he has a letter to the same effect, and this is the government's equivalent of Athe check's in the mail@ I guess.

[Applause]

DR. GOLDSTEIN: Yes, I guess it will show up depending on how we do today.

Before we get started, there are a couple of other things. One, and a critical thing for the committee, fill out your lunch things. You know, that worked incredibly smoothly yesterday and we have a big group and we have to

make sure the same thing happens. The second thing is to make sure your little nameplates are pointed in this direction so that we can see them.

Third thing, for the members of the public that are here, very often emotions can run high during these type of proceedings. Please, no applause, no cheering, no clapping.

The last thing, just before we get going, is that we had a full schedule yesterday. Today's schedule, if anything, is fuller, with more issues and more complicated issues to discuss and a longer list of questions that we need to try to get through. The way I did it yesterday is that for some of the items, when I thought we didn't need to have a formal vote, I just asked for a consensus show and I will try to do the same thing again today. Again, if people want a formal vote on some items that I thought should be consensus, we will go ahead and do that. But if we took formal votes on each item we would start now and we would never get done.

So, having said that, we will now begin with the industry presentations. Unlike yesterday where the FDA stipulated that the drug was efficacious for the indication

that we were discussing, the FDA has not stipulated that today so we have to deal not only with all the issues of toxicity that we dealt with yesterday but the issue of efficacy as well. So, having said that, let's get the ball rolling. Dr. Cunniff?

Industry Presentation

Sabril (vigabatrin) for Oral Solution for Infantile Spasms

Introduction

DR. CUNNIFF: Dr. Goldstein, Dr. Temple, Dr. Katz, Dr. Chambers, members of the advisory committee, members of the FDA review team, ladies and gentlemen, good morning.

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My name is Tim Cunniff and I head the regulatory affairs, pharmacovigilance and clinical quality assurance divisions for Ovation Pharmaceuticals. This is the second and final day of our advisory committee meeting for Sabril. Yesterday the committee heard presentations pertaining to the refractory complex partial seizures indication. Today we are going to continue our discussion of vigabatrin for use in a separate patient population, namely, patients with infantile spasms.

[Slide]

A brief summary of yesterday's meeting is shown here. The committee recommended approval of Sabril for adjunctive treatment of refractory complex partial seizures in adult patients who had failed to respond to several other AEDs. The committee advised that the approval be accompanied by a risk evaluation and mitigation strategy, and we got a lot of good advice yesterday over the risk management tools we should be using and risk communication to assure safe use of Sabril.

Due to the potential for a clinically meaningful loss of vision, the committee also recommended that ophthalmologic assessments be performed at baseline, at 3 months prior to maintenance phase treatment, every 4 to 6 months thereafter, and at a time point following drug discontinuation.

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Before we begin today's presentation it is important to understand some special characteristics for the patient population with infantile spasms. Fortunately, the number of patients with IS in the United States is very small and the annual incidence is only about 2,500 patients. This is also a pediatric disease as most patients with IS

are less than 3 years of age.

There are no approved therapies for infantile spasms in the United States, and the other agent used routinely is not effective for all patients and also has a side effect profile that can limit its use.

It is difficult to conduct clinical trials in patients with IS due to the lack of adequate numbers of patients for this orphan condition, also the inability to conduct prolonged placebo-controlled studies due to ethical issues, and the resulting short observation period in which to establish efficacy. Finally, the treatment goal for infantile spasms is complete cessation of spasms versus a reduction in seizure frequency in patients with complex partial seizures.

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The formal proposed indication is shown here. We are requesting approval for Sabril as monotherapy for the treatment of pediatric patients with infantile spasms.

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Although an unapproved drug in the United States, Sabril is widely available in most major countries throughout the world including Canada, Mexico, the European

Union and other countries in Asia, Latin America, Africa and the Middle East. We estimate that more than 1.5 million patients have received vigabatrin since initial marketing approval in Europe over 19 years ago.

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We went through the development and approval history of vigabatrin yesterday so I will not cover it in great detail today. With respect to infantile spasms, however, I will note that the largest clinical trial in this patient population ever conducted opened in 1995 under an investigator-sponsored IND.

The study serves as one of our pivotal clinical trials to establish the efficacy of vigabatrin for infantile spasms. In 2000 the FDA granted Orphan Drug status to vigabatrin for infantile spasms. Ovation acquired the North American rights to vigabatrin in 2004 and a license to the data from the large investigator-sponsored clinical trial I just mentioned at the same time.

In late 2006 a report of MRI abnormalities in 3 of 15 treated vigabatrin patients with infantile spasms prompted the FDA to request additional information. Ovation gathered, summarized and submitted this information to FDA

in late 2007, and in 2008 the FDA accepted the infantile spasms NDA for review.

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There are some key considerations to keep in perspective today. First and foremost, infantile spasms is a severe and catastrophic form of epilepsy and there exists an unmet medical need. Additionally, there are no drugs approved for this condition in the United States.

There are a good number of clinical trials that establish the efficacy of vigabatrin in the treatment of infantile spasms, including data from the largest clinical trial ever conducted for this orphan indication. These trials all demonstrate a significant benefit in favor of vigabatrin in achieving protocol-specified endpoints for spasm cessation. The safety profile of vigabatrin is also well characterized by numerous clinical trials and substantial postmarketing experience.

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With respect to the peripheral visual field defect, many essential features are now better understood since this issue was first identified ten years ago. The estimated prevalence for pVFD is fairly high and the risk

appears to increase after prolonged exposure to vigabatrin, and on average is reported many months after therapy is initiated. If pVFD occurs, it is usually mild to moderate in severity, appears to progress slowly and is irreversible. Age appropriate ophthalmologic testing can detect pVFD and our monitoring recommendation is meant to prevent a clinically meaningful restriction in a patient's peripheral vision.

Transient MRI abnormalities reported recently in infants with infantile spasms are without reported clinical sequelae and appear to be reversible in a majority of patients. However, Ovation has agreed to conduct a long-term longitudinal study as a post-approval commitment to further characterize the clinical relevance of this finding. The study will also assess long-term neural development and cognition.

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As discussed yesterday, to further mitigate risk Ovation will provide a comprehensive risk evaluation and mitigation strategy, or REMS, that will accompany the approval of vigabatrin to ensure that the drug is used safely by appropriate patients. Many risk management tools

will be incorporated into our REMS, including informative labeling, communication and educational programs and several restrictive elements to ensure safe use, including a mandatory registry.

Finally, I can't stress enough that one must consider the benefit of eliminating infantile spasms in vigabatrin-responsive patients versus the risk for pVFD and MRI abnormalities. The evidence we will present today establishes a positive benefit to the risk profile for vigabatrin in the treatment of patients with infantile spasms.

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The rest of today's agenda is shown here. Dr. Don Shields, from UCLA, will present information on infantile spasms and the unmet medical need. Dr. Steve Sagar will present the efficacy and safety data, including the peripheral vision field defect, in patients with IS. Dr. Reid Patterson, an independent consultant, will discuss findings from the juvenile toxicology studies. Dr. Jim Wheless, from the University of Tennessee, will describe MRI abnormalities observed in vigabatrin-treated patients with infantile spasms. I will return to briefly summarize our

proposed Sabril REMS that we discussed in detail yesterday. Finally, Dr. Jack Pellock, from the Virginia Commonwealth University, will conclude our presentation with an overall benefit/risk assessment.

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In addition to today's speakers we have outside consultants available to answer any questions you may have. I would now like to invite Dr. Shields to the podium to discuss infantile spasms and the unmet medical need for this condition. Thank you.

The Unmet Medical Need

DR. SHIELDS: Thank you and good morning.

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My name is Don Shields and I am Director of the Pediatric Epilepsy Program at UCLA. For those of you not familiar with infantile spasms, I will give a brief overview of this unique pediatric disorder.

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I will discuss the disease background of infantile spasms, including characteristics that make it such a distinctive disorder; a brief overview of causes and currently available treatments; and the outcome for the

unfortunate children who develop infantile spasms.

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There is an interesting dichotomy in children who develop seizures at a very young age. They tend either to be very benign disorders such as febrile seizures or disorders characterized as catastrophic, that is, they have an important long-term impact on development, and infantile spasms is at the top of that list. The Aeverything else@ category includes complex partial epilepsy, which is much less common in children and young children than it is in adults and the severity is between the benign and catastrophic. Fortunately, that catastrophic category is a relatively infrequent disorder.

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There are two defining characteristics of catastrophic epilepsy. The first is that this is a pediatric problem. Most of the patients with catastrophic epilepsy begin their seizures very early in life, usually in the first year, and mental retardation is a common consequence and that is what I would believe to be the catastrophe associated with it.

Infantile spasms is the preeminent disorder in

that category. With only about 2,500 patients a year, it is pretty uncommon. However, the seizures and the EEG are characteristically very distinct from other seizure disorders. Unfortunately, the seizures are often difficult to control.

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What are the distinct features of infantile spasms? Dr. West described infantile spasms in 1841 in a letter to the editor in Lancet, and I have included elements of his report here since it is one of the best descriptions I have ever seen. It characterizes the age, the semiology and the outcome of a patient who was his son, and it was a cry for helpB-what am I going to do for my child?

The child was now a year old, was a remarkably fine, healthy child when born and continued to thrive until he was 4 months old. It was at this time that I first observed slight bobbings of the head forward. These bobbings increased in frequency and strength causing a complete heaving of the head forward towards his knees. These would be repeated ultimately at intervals of a few seconds and repeated 10, 20 or more times at each attack. He sometimes has 2, 3 or more attacks in a day.

[Video presentation for the committee]

So, this is a child having infantile spasms. That is a spasm. There is another one. You will note that they are not the rhythmic things that you see with other seizure disorders. It certainly doesn't have the dramatic appearance of somebody having a grand mal seizure, but the significance for this child is greater than the significance for somebody having the seizure that we saw yesterday. So, as we shall see, the subtle appearance of the spasms belies the significance to the child, as noted in this heading, Alittle seizures, big consequences.@

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To continue Dr. West's description, independent of this affliction is a fine, grown child but neither possesses the intellectual vivacity or the power of moving his limbs of a child his age. He never cries at the time of the attacks, or smiles, or takes any notice but looks placid and pitiful. Yet, his hearing and vision are good. This description of the developmental regression and delay is, unfortunately, typical for uncontrolled infantile spasms, again, a developmental catastrophe.

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As previously mentioned, another characteristic feature is the EEG. This is a patient with infantile spasms. This is an example of hypsarrhythmia. This is an exceedingly abnormal, highly disorganized, very high voltage EEG. If the settings were the same as a standard EEG those peaks and valleys would be covering the entire page so the scale is toned down so that you can't tell how great it truly is.

As soon as I see a new patient with infantile spasms, or if a physician calls me with a diagnosis of infantile spasms, I arrange admission to the hospital to begin the evaluation and to initiate treatment.

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We generally define etiology into three categories. First is idiopathic. These are patients who were previously normal and had no identifiable cause. This is what is called West syndrome in honor of Dr. West.

Cryptogenic where the children may not have been quite normal. They develop spasms. We do the work-up and don't find an etiology. That makes it cryptogenic.

In patients where we can find an etiology it is classed as symptomatic. Tuberous sclerosis is one of the

most common symptomatic etiologies and that symptomatic category represents about 70-75 percent of our patients.

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The next question is how do we treat them. As previously noted, there are no FDA-approved medications. That doesn't mean we don't have medications that we can use. There are still drugs, those 2 listed there, that we use.

As very distinct from other disorders, complete control of seizures and resolution of hypsarrhythmia is the definition of success. Say, 50 or 90 percent reduction in the seizures is not considered sufficient. We have to get complete control if we are going to have a chance to improve the development, and that really is the ultimate goal. Stopping seizures is nice; improving development is really what we want to do.

There is some evidence that valproic acid may be helpful but children under 3 have an increased risk of liver failure so we try not to use it in that age group. The other medications all have some evidence of efficacy but none of them rise to the level of suggesting that they are first-line therapies. Even nitrazepam on that list, which has some evidence of efficacy, is associated with an

increased risk of death in young children.

So, there are several medications in use. Only 2 of them are really considered effective by most child neurologists, ACTH and vigabatrin. Neither of these medications is currently approved by the FDA to treat this disorder but both are really important for our ability to treat children who have infantile spasms.

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Just to give a quick overview of the 2 medications, ACTH is given by intramuscular injection. The parents have to be taught to give that so they give daily or sometimes twice daily injections. The current recommendation is to give a high dose at the beginning to maximize efficacy, but take them off quickly to minimize the long-term side effects which are significant, including the development of a cushingoid appearance, stress ulcers, immunosuppression, hypertension, hyperglycemia, irritability, increased appetite and weight gain.

Vigabatrin is easier to use. It is a soluble powder given orally. We can rapidly titrate, typically up to 125-150 mg/kg. Generally, if it is effective, it is effective in the first 2 or 4 weeks. If it is effective,

there is still discussion about what the long-term duration of therapy should be but somewhere between 3-12 months is probably where it should be. There are key side effects which will be discussed. Peripheral field defect and MRI changes and sometimes drowsiness is also present.

It is important to note that neither therapy could really be considered low risk and because of that these children are really followed quite frequently in our clinics.

[Slide]

Vigabatrin is considered an important therapeutic option throughout the world. Looking at treatment guidelines specifically related to infantile spasms in the AAN and CMS practice parameter, steroids are considered as probably effective. That is really ACTH. And, vigabatrin is possibly effective for IS and infantile spasms due to tuberous sclerosis.

That is the highest level that any drug gets in this analysis and it is not because we don't know about the drugs or don't know how to treat the patients, it is because the disease is sufficiently uncommon that the kinds of studies required to get to the higher levels just have not

been done and are not available.

Treatment guidelines in the United Kingdom, the SIN, or the Scottish program, indicates that vigabatrin is superior where infantile spasms are secondary to TS. In the NICE program, which is the National Institute of Health in the U.K., it is first-line therapy. In expert opinion in Europe, it is the treatment of choice for spasms. In the U.S. ACTH and topiromate are considered first-line. Vigabatrin is sometimes appropriate, especially for treatment of tuberous sclerosis.

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I would like to move on to another issue to illustrate the length we would go in order to control a child who has infantile spasms. This is an MRI image from a young child who presented at 6 months with infantile spasms. It was clear that he had unilateral problems. His spasms failed to respond to medical therapy but his parents, understandably, were resistant to the concept of a surgical procedure, which is where we were going with this case. The left hemisphere is not normal.

This is an MRI scan taken at 15 months. The hemisphere on your left, the right hemisphere, is

myelinating. The one on the right is not myelinating, and this is an indication of cortical dysplasia, a developmental abnormality.

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At 18 months, having failed medical therapies, this young man underwent a surgical procedure called hemispherotomy. The entire left hemisphere was removed or functionally disconnected. The arrows are pointing to places of disconnection.

As a result of this surgical intervention, he has a right hemiparesis and a right visual field cut so he cannot see anything in the right visual field area. However, his spasms were completely controlled.

This case comes from several years ago, and the benefit for this young man is that he has had an excellent developmental outcome. He has now graduated from high school and is going to junior college, studying to be a writer, which is really interesting considering we took out his dominant hemisphere. The opportunity for recovery is remarkable in these young children if the spasms are controlled.

At 18 months, before he was operated on, this boy

had no awareness. He had no apparent interaction with anything going on around him. You might give him a developmental quotient of 20 at that point, which might roughly relate to an IQ of 20, and he was a developmental catastrophe. But over the next several years he gradually moved closer and closer into the normal range until the time he was in high school when he was truly in the normal range.

This case is not presented to tout surgery but to make a specific point, and that is that producing visual field defect, as well as hemiparesis, is considered acceptable as a price to pay for the chance to give the child a more normal development.

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Let’s regard the outcome in uncontrolled infantile spasms generally evolved through other seizure types between 1 and 2 years of age, such as Lennox-Gastaut syndrome or intractable partial seizures, and 6-33 percent of patients die by age 3. It is probably really closer to the 6 percent than the 33 percent at this time. About a third become autistic, and 70-90 percent are intellectually developmentally delayed, often with IQs in the 30-50 range.

The key issue is that the children who eventually

have normal intelligence or near normal intelligence were the ones who had their spasms controlled early on. The time to initiation of treatment and control of spasms appears to be quite significant in that developmental outcome.

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There are a few studies that illustrate improved developmental outcome with more timely intervention. I will discuss two, one using treatment with ACTH and one using treatment with vigabatrin.

In this study 37 percent were treated with an ACTH followed by prednisone regimen. Early treatment was defined as treatment that began within 1 month of the onset of spasms. One hundred percent of the patients in that early treatment group achieved a normal outcome, which is defined as an IQ greater than 70, compared with only 40 percent in the late treatment group.

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The second was a retrospective study of infantile spasms caused by tuberous sclerosis, and of the 50 patients studied, 36 percent had an IQ greater than 70. The authors identified 3 factors that were correlated with the poor developmental outcome. The first was an increased time

between onset of spasms and spasm cessation. Every month of delay represented 1.09 increase in odds.

So, it was cumulative month to month, to month, to month. The longer it went, the worse it became. The delay between treatment initiation and spasm cessation was also significant, as was evolution to other seizure types which was very significant. But these reports indicate that early and effective treatment is important for out patients.

[Slide]

I view infantile spasms as the archetypical catastrophic childhood epilepsy. In distinction with some of the other catastrophic epilepsies, however, infantile spasms patients have the potential for a normal or at least substantially improved development if the spasms are controlled.

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In summary, patients with infantile spasms are at risk for significant morbidity and mortality. The consequences, of course, extend beyond the pt. We have not really discussed this, but if you can imagine watching your own child having dozens or even hundreds of seizures a day and then regress development, it is clear that the

consequences for the family are enormous.

There is clearly an unmet need. The current therapies that have demonstrated efficacy, either surgical or medical, all have potential or perhaps even certain adverse effects or consequences, but the risk/benefit ratio in these patients favors such aggressive therapy. Worldwide and current U.S. guidelines support vigabatrin as an important therapeutic option for these patients.

Dr. Steve Sagar will now discuss the efficacy.

Efficacy and General Safety

DR. SAGAR: Good morning.

[Slide]

My name is Steve Sagar. I am the medical director for vigabatrin at Ovation Pharmaceuticals. For those of you who were not here yesterday, I would like to begin with a brief review of the clinical pharmacology of vigabatrin.

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As was discussed yesterday, the available evidence supports the unique mechanism of action for vigabatrin. Vigabatrin is an irreversible inhibitor of GABA transaminase.

This schematic shows 2 CNS neurons and their

intervening synapse. GABA is released into the synapse and its action is terminated by being taken up into presynaptic nerve endings and into surrounding glial cells. It is then metabolized to succinic semialdehyde by GABA transaminase.

Vigabatrin irreversibly blocks GABA transaminase, leading to an increased concentration of GABA at the synapse. GABA is the primary inhibitory nerve transmitter in the central nervous system and it is the inhibitory activity of GABA that presumably mediates the antiepileptic action of vigabatrin. Vigabatrin is the only drug among currently available AEDs that has this mechanism of action.

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The pharmacokinetics of vigabatrin are quite predictable with almost complete oral absorption, linear dose proportional pharmacokinetics and no relevant effects of food, age, gender, race or disease state. Vigabatrin is not protein bound and is renally excreted without undergoing metabolism and, hence, is free of clinically relevant drug-drug interactions.

This pharmacologic information is primarily from healthy adults, and there is limited pharmacokinetic information from the infant population. However, we do know

that clearance of vigabatrin is increased in infants as compared to adults, as one would expect for a drug that is renally eliminated. The pharmacologic effects of vigabatrin are not correlated with plasma levels, the cause of the mechanism of action as an irreversible enzyme inhibitor.

[Slide]

Here is an overview of what I will discuss today. I will discuss vigabatrin's clinical development program, as well as general tolerability as demonstrated by the adverse event profile in clinical trials. Two special safety topics, the retinal effects of vigabatrin and MRI abnormalities will be discussed separately. I will discuss the first of these. Then Dr. Reid Patterson will discuss preclinical findings of intramyelinic edema in animals, and Dr. James Wheless will discuss the vigabatrin-associated MRI abnormalities seen in some infants treated for infantile spasms.

First we are going to review the clinical development program for infantile spasms, including controlled trials, uncontrolled trials and additional supportive literature.

[Slide]

By way of background, as touched on by Dr. Cunniff, there are key differences in designing clinical trials for infantile spasms as compared to other forms of epilepsy, including complex partial epilepsy which we discussed yesterday.

First, infantile spasms is, fortunately, a rare condition. The estimated incidence, as you have heard, is 2,500 cases per year in the U.S. Therefore, clinical trials generally contain small numbers of subjects. Prolonged placebo-controlled trials are not feasible in this disease because clinicians are unwilling to withhold effective therapy for this catastrophic disease.

Yesterday, for CPS we examined adjunctive therapy for patients who have failed prior treatments, whereas the data I will present will mainly discuss monotherapy for infantile spasms. Also, the relevant observation period for infantile spasms is short, 2 to 4 weeks. Infants who respond to treatment respond quickly and physicians do not want to maintain a patient on ineffective therapy.

Although seizure freedom is always the goal of epilepsy therapy, in CPS decrease in the frequency of seizures without complete seizure control may still make a

difference in the quality of life of the patient, however, in infantile spasms, as Dr. Shields has noted, complete cessation of spasms is the clinically relevant outcome as it appears to correlate with improved neurologic function and developmental outcomes.

Finally, in clinical trials of therapy for infantile spasms investigators try to build EEG confirmation into the trial design both as an objective confirmation of seizure control, and as an independent indicator of brain function.

[Slide]

This slide provides a summary of the results of the 3 infantile spasms control trials I will discuss today. Spasm cessation was achieved in each trial with a rapid onset within 2 to 4 weeks. Additionally, consistent efficacy was demonstrated in secondary outcomes including general well being and global assessments. I will now discuss the 3 trials separately.

[Slide]

This slide is a schematic of study 1A, the largest controlled trial ever conducted in infantile spasms, and 227 patients were randomized, of which 221 met criteria for the

modified intention-to-treat cohort. Study 1A was an investigator-initiated study initially intended as a compassionate-use trial but, after consultation with the agency, it was changed to a randomized trial in which infants with newly diagnosed infantile spasms were randomly assigned to 2 doses of vigabatrin.

There was a low dose group of 18-36 mg/kg/day orally and a higher dose group of 100-148 mg/kg/day. After a single-blind treatment period that could last from 14-21 days the subjects entered a flexible dose, open-label treatment period that lasted as long as 3 years.

The primary endpoint for this study was spasm cessation for 7 consecutive days as determined by caregiver observation. The period of spasm cessation was required to begin within the first 14 days of therapy and be confirmed by a video EEG recording within 3 days of the end of the 7-day spasm-free period. It should be emphasized that this is an extremely rigorous outcome measure.

[Slide]

By this primary protocol-specified outcome criteria subjects in the high dose group achieved a greater rate of spasm cessation than the low dose group, and the

difference was statistically significant. By this criterion, 15.9 percent of the high dose group achieved spasm cessation as compared with 7.0 percent in the low dose group. Although statistically significant, these numbers are low, one reason being that the 3-day window for video EEG confirmation of the response proved infeasible for a substantial proportion of the subjects.

Therefore, an ad hoc analysis was performed to allow a broader window for EEG confirmation. If the time window for EEG confirmation is broadened 31 percent of the high dose group achieved spasm cessation compared with 13 percent of the low dose group. I would like to emphasize that these observations of spasm cessation were made within 21 days, speaking to the rapid onset of efficacy of vigabatrin.

Regardless of how the data are analyzed, the study shows that vigabatrin can produce spasm cessation in IS patients that is rapid in onset and that has a rate that is clinically meaningful.

[Slide]

In study 1A vigabatrin was effective in all 3 etiologic groups into which subjects were classified,

cryptogenic, symptomatic and in the subgroup of symptomatic patients with tuberous sclerosis. In the overall clinical trial experience there is a trend for vigabatrin to be more effective in the tuberous sclerosis group of subjects than in other subgroups but it has demonstrated efficacy across all etiologies.

[Slide]

To summarize study 1A, vigabatrin is effective as monotherapy of newly diagnosed infantile spasms. Doses greater than 100 mg/kg/day are more effective in achieving spasm cessation than doses lower than 50 mg/kg/day. Vigabatrin has a rapid onset, within 2 to 3 weeks, and vigabatrin is effective across etiologies.

[Slide]

The agency has questions about the chronology of study 1A which I would like to address. On this slide is a timeline of major events during the study. As I mentioned before, study 1A was initially intended as a compassionate-use safety trial, and throughout the study investigators continued to be motivated by a desire to make vigabatrin available for their patients with infantile spasms.

The most important point I would like to make is

that Ovation acquired the data for this study in 2004, after the study had been completed. Ovation performed an independent, complete source data verification and data analysis. The results of that analysis was what I presented here today, and it was performed completely independently of the investigators. I should say that Dr. Shields, along with Dr. Edelman, were the principle investigators and designers of this study.

There are 3 other issues that require clarification. First, in the first protocol the sample size was set at 44. As that number of enrolled subjects was approached the investigators, wanting to keep the study open, consulted with the FDA and agreed to an increase in sample size to 150. By the time this protocol amendment was actually approved, 64 subjects had been enrolled. The increase in sample size did increase the statistical power of the study but that was not the primary motivation of the investigators in changing the protocol.

There were two interim analyses of the data, both of which were carried out at the request of the sponsor but neither of which was specified by the protocol. The first interim analysis was performed to provide the sponsor safety

and dosing data for infantile spasms to submit to their NDA. It was not done with any intention of stopping the study or altering the conduct of the study in any way.

The second interim analysis was thought by the investigators to be the final formal efficacy analysis to be performed, although the investigators intended to keep the study open, again, hoping to be able to continue making the drug available to their patients. The second interim analysis was published in the AJournal of Neurology@ in 2001. The differences between the Ovation analysis and the Neurology publication are due to the application of a very stringent definition of spasm cessation in the Ovation analysis.

Subject enrollment was terminated in 2000 when the sponsor indicated to the investigators that it was withdrawing support, and the study was formally ended in September, 2001. The last patient completed follow up in April, 2002.

[Slide]

I will turn now to study FR03. This was a multicenter study, conducted in France. It was limited to infantile spasms associated with tuberous sclerosis.

Twenty-two evaluable subjects were randomly assigned to receive either vigabatrin or hydrocortisone during the first 4-week phase. During the second 4-week phase, those patients who responded were to be maintained on the same treatment to which they were initially randomized and those who did not respond were to be crossed over to the other treatment. The primary outcome of this study was the proportion of subjects in each group achieving spasm cessation.

[Slide]

The results of the study are summarized in this schematic. Within the first 4 weeks of treatment all 11 vigabatrin-treated patients achieved complete spasm cessation. During the same time frame, 4 of the 11 hydrocortisone-treated patients achieved complete spasm cessation. This difference, despite the small number of subjects, was highly statistically significant. During the second 4-week phase the remaining 7 hydrocortisone patients were switched to vigabatrin and all 7 achieved spasm cessation within 4 weeks.

So, in this study, which was limited to tuberous sclerosis patients, all subjects achieved spasm cessation,

18 with vigabatrin and 4 with hydrocortisone.

[Slide]

The secondary endpoints in FR03 show that the majority of patients had markedly improved general well being and statistical and significant improvements in behavior. EEGs were performed in the study at 2 months after starting therapy. The EEG outcome is confounded by missing data and hydrocortisone patients crossed over to receive vigabatrin but the large majority of subjects had EEGs judged to be improved.

[Slide]

To summarize, study FR03 substantiates the effectiveness of vigabatrin as monotherapy for infantile spasms associated with tuberous sclerosis. The onset of efficacy was rapid and, importantly, patients who failed to respond to hydrocortisone responded to vigabatrin. Additionally, patients with infantile spasms showed marked improvements in global assessments of function.

[Slide]

The third controlled study I am going to discuss is W019. This was an international, double-blind, placebo-controlled trial with a very brief, 5-day, placebo-

controlled treatment period. Forty patients were randomized to receive placebo or vigabatrin which could be escalated in dose depending on response.

By protocol, vigabatrin subjects were to be treated with doses of 100-150 mg/kg/day by day 8, comparable to the high dose group in study 1A. One subject, a protocol violation, actually received 200 mg/kg/day.

The 5-day treatment period was followed by a 6-month open label period in which 36 of the 40 patients continued to receive vigabatrin. The primary protocol-specified outcome measure was average percent change in frequency of spasms as assessed in a 2-hour sampling window each day during the final 2 days of the double blind period.

As the study was first designed, it was anticipated that the 2-hour window would be representative of the overall clinical condition of these patients. During the actual conduct of the study, however, it was observed that the narrow observation window was inappropriate as it did not, in fact, represent the daily spasm rate. A secondary outcome measure used a 24-hour observation period instead.

[Slide]

Based on the 2-hour observation window there was no statistically significant difference between placebo and vigabatrin, as shown here. However, as the observation window expanded to 24 hours vigabatrin-treated patients displayed a greater reduction in spasm frequency, 68.9 percent as compared to placebo-treated patients, 17 percent. This difference was statistically significant.

[Slide]

As has been noted, however, complete spasm cessation is a more clinically relevant measure of efficacy than reduction in spasm frequency for infantile spasms. The data shown here demonstrated that vigabatrin-treated patients achieved a higher rate of spasm cessation, defined by the investigators of this study as either 0 or 1 spasm for 24 hours at the end of the double-blind phase.

When complete spasm cessation was measured, not allowing even 1 spasm per 24 hours, 35 percent of vigabatrin-treated patients, compared to 10 percent of placebo-treated patients, achieved this milestone by day 8. However, this difference did not reach statistical significance. Consistent with the prior two studies discussed, the achievement of spasm cessation in study W019

occurred within 2 weeks and was associated with improvements in the EEG pattern.

[Slide]

To summarize study W019, although the protocol-specified outcome employed an unrepresentative observation window and, hence, did not reach statistical significance, vigabatrin was demonstrated to be effective in achieving spasm cessation in this placebo-controlled trial. Also, in responders the onset of efficacy occurred in less than 2 weeks.

[Slide]

In reviewing the long-term benefits of vigabatrin for patients with IS, during the open-label follow-up phases of the three studies discussed we see here evidence that a substantial fraction of patients maintain spasm cessation for long periods.

Also, for formal assessments of developmental status before and after treatment are available in studies FR03 and W019 scores were improved or no worse after treatment. These data showing spasm cessation and developmental outcomes demonstrate that vigabatrin provides long-term benefits.

[Slide]

The three controlled trials, as has been discussed, are quite consistent in that vigabatrin as monotherapy can achieve spasm cessation in 31-100 percent of patients, with a rapid onset within 2-4 weeks. In addition, secondary endpoints in long-term analyses further support the efficacy of vigabatrin treatment for patients with infantile spasms.

[Slide]

Two uncontrolled studies submitted with the NDA further support the efficacy of vigabatrin for patients with infantile spasms. Study 332.5 was an open-label, single-center study designed to evaluate the safety and efficacy of vigabatrin as adjunctive therapy in infants and children with drug-resistant IS. Subjects were 1-12 years old and had failed prior medical treatment for infantile spasms.

In this trial 46.5 percent achieved complete seizure freedom, even in this population with demonstrated treatment resistance. The study of adjunctive therapy is consistent with findings from the controlled clinical trials of vigabatrin as monotherapy.

[Slide]

Study 3E01 was a retrospective analysis, conducted in 59 centers and 11 European countries. Data were obtained from the records of patients diagnosed with infantile spasms who had been given vigabatrin as their initial treatment for IS. Sixty-eight percent of these patients achieved complete spasm cessation, again supporting the overall efficacy findings of vigabatrin.

[Slide]

There are multiple other published studies of varying design that have confirmed the efficacy of vigabatrin as monotherapy of this severe form of epilepsy. Of these, 5 informative publications are listed on this slide. These studies were all performed in Europe. The rates of spasm cessation for the first 4 studies listed were after short-term treatment and were 38-54 percent of subjects achieving rapid onset of spasm cessation.

I would like to call special attention to the 2 publications by Lux, et al., at the bottom of the list. These papers report results of the United Kingdom infantile spasms study, or UKISS, a multicenter, randomized trial comparing vigabatrin with hormonal therapy for newly diagnosed infantile spasms.

[Slide]

UKISS randomized 107 newly diagnosed IS patients to receive either hormonal therapy, which could be either oral prednisolone or an injected synthetic ACTH analog. The first point I would like to make is that within the first 2 weeks of therapy 54 percent of vigabatrin-treated infants achieved spasm cessation, and by 14 months of age 75 percent were spasm free.

The second point is that the UKISS study excluded infants with tuberous sclerosis, the group in which vigabatrin may be most efficacious. Therefore, there is demonstration that vigabatrin is efficacious across etiologies of infantile spasms.

A third and extremely important point is that following day 14, when the patients were treated according to their treating physicians, of the 55 patients initially randomized to hormone therapy 27 took vigabatrin because of failure of initial response to hormonal treatment and in the remainder because of seizure relapse. This reinforces the need for multiple therapies to be available for these infants. These published studies support the consistent thread of evidence of the efficacy of vigabatrin seen in

both controlled and uncontrolled studies.

[Slide]

In summary, vigabatrin is effective as monotherapy of infantile spasms. The benefit is demonstrated by spasm cessation, EEG confirmation and secondary outcome measures, including assessments of global function. Vigabatrin is effective across etiologies of infantile spasms and has a rapid onset of efficacy, generally within 2-4 weeks. Spasm cessation has been maintained over long periods of time, as demonstrated in 3 controlled clinical trials and published literature. Importantly, where we have data, spasm cessation is associated with improved developmental outcomes.

[Slide]

We are now going to discuss the safety of vigabatrin in the treatment of infantile spasms. First I will discuss the adverse events in clinical trials and then we will return to special safety issues. I will review the experience from the 3 controlled clinical trials, 1A, FR03 and W019.

Your briefing document provides additional data from uncontrolled trials as well as from trials in epilepsy

that included subjects less than 3 years of age. These additional populations do not significantly add to the clinical trial safety profile of vigabatrin so I will focus on the data from the controlled trials.

[Slide]

There were a total of 261 patients in the safety population of the 3 controlled trials. The most common adverse events in these trials are shown here. The majority of these events are common pediatric medical conditions and are expected in a group of infants.

In addition, irritability, somnolence, sedation and insomnia were reported. These have been seen with vigabatrin in other indications and are also reported in the postmarketing database. These are common side effects of many antiepileptic drugs.

[Slide]

Serious adverse events are tabulated on this and the following slide. The most frequent serious adverse events were infections and central nervous system disorders, including complications of severe epilepsy.

[Slide]

This is a continuation of the tabulation of

serious adverse events. Again, the infections that one would expect in this patient population are prominent on the list.

[Slide]

Eight deaths have occurred in the clinical trial population. Four deaths occurred in controlled trials, to give a full accounting of the clinical trial experience. Four deaths reported in the retrospective study 3E01 are also listed. The causes are listed here and were not thought to be related to vigabatrin treatment by the investigators conducting the studies. The occurrence of 8 deaths among 511 patients is consistent with the high mortality rate from the underlying diseases associated with infantile spasms.

[Slide]

The postmarketing global safety database includes 132 adverse event reports from patients less than 2 years of age treated with vigabatrin. The most common adverse events in these reports are listed, abnormal brain MRI, which Dr. Wheless will discuss in detail; agitation; hypotonia; somnolence and encephalopathy, again consistent with clinical trial data and experience with other AEDs.

[Slide]

To summarize, infantile spasms is a catastrophic disease. It significantly impairs the neurologic development of infants. Vigabatrin offers an effective treatment, as evidenced by data from controlled and uncontrolled clinical trials. Vigabatrin is generally well tolerated. The safety profile is well characterized and is similar to other antiepileptic drugs.

[Slide]

There are two special safety issues which we will now address, the retinal effects of vigabatrin and MRI changes associated with the drug. I will address the first of these.

[Slide]

As we discussed yesterday, in adults and children treated for CPS vigabatrin can cause a peripheral visual field defect as can be demonstrated directly by quantitative perimetry. In infants, however, testing vision is even more challenging than in adults. Confrontation testing can be performed in virtually all children, including infants, and ERG has provided an important research tool that can also be used as a clinical tool in appropriate circumstances.

[Slide]

Confrontation visual field testing in infants is carried out by showing them attractive visual targets such as toys, as is being done with this toddler. The examiner observes if the child visually fixates on the target. In the hands of an experienced examiner this is a useful test but is qualitative and qualitative perimetry is not possible in children less than 8 or 9 years old.

[Slide]

The electroretinogram is a quantitative test that can be performed in infants as well as older children and adults. In infants it usually requires sedation, typically with chlorohydrate, as it requires a contact lens electrode to be placed on the cornea. The retina is stimulated with a full-field flash of light with a device known as a Ganzfeld stimulator and the response of the retina is detected with the corneal electrode.

Some general conclusions from the literature concerning ERG are stated here. The ERG measures which correlated best with the vigabatrin-induced peripheral visual field defect in adults are the 30 Hz flicker amplitude and the cone b-wave amplitude. Although it is not

routinely done, it is possible to measure the ERG response from localized regions of the retina and that demonstrates, as one would expect, that the ERG generated by the peripheral retina is more affected by vigabatrin than the central retina. Visual evoked response latencies which reflect optic nerve and optic pathway conduction are normal.

Importantly, the ERG matures during infancy. As the retina is immature at birth and the ERG does not reach the adult characteristics until 3-5 years of age, therefore, during infancy ERG measures must be compared to age-matched controls.

[Slide]

The most extensive clinical database available is from the laboratory of Dr. Carol Westall at the Hospital for Sick Children in Toronto. She and her colleagues have performed serial ERG examinations in over 200 infants treated with vigabatrin for infantile spasms. The study design is outlined on this slide. Ovation is the major sponsor of this ongoing research.

I will present data from 246 subjects, of which 181 had more than 1 examination. An abnormality is defined as a finding of more than 2 standard deviations from the

mean of age-matched, healthy controls.

[Slide]

Some of the findings of the Toronto study are summarized on this slide. The prevalence and incidence figures are for sustained abnormality, that is, an abnormality present on the final 2 consecutive examinations and, hence, presumed to be permanent. The period prevalence is 31 percent.

The incidence of just over 15 cases per 100 patient-years is based on subjects who were free of ERG abnormality at baseline. Note that there is a high background rate of ERG abnormality in this population. Over one-third of infants with IS have abnormal ERGs as compared to age-matched controls before exposure to vigabatrin.

The incidence and prevalence are somewhat higher than seen for peripheral visual field defect in adults. There are at least 3 possible explanations for this difference. Infants with infantile spasms are typically treated with 2-3 times the dose per kilogram body weight than is used to treat CPS. The infant retina may be more susceptible to the effects of vigabatrin than the adult, or the ERG may be more sensitive to early changes than

perimetry.

[Slide]

This table shows more detailed incidence data. The first thing to note is that the 30 Hz flicker amplitude appears to be a more sensitive indicator of the retinal effects of vigabatrin than cone b-wave amplitude. Second, of those subjects free of abnormality at baseline, half have an abnormal 30 Hz flicker amplitude at some time during the study, and in one quarter that abnormality is sustained and presumably represents a permanent defect that will likely correlate with a peripheral visual field defect later in life.

[Slide]

For the 19 subjects who had replicated abnormalities, that is, abnormalities on 2 consecutive examinations, the median duration of vigabatrin exposure at their first abnormal examination was 12.5 months and the range was 3.1 months to over 5 years.

[Slide]

This is a plot of the cumulative percentage of subjects who had normal ERG at baseline but developed an abnormality during treatment. The cumulative percentage is

plotted versus time on vigabatrin. Less than 15 percent have an abnormal ERG after 6 months of exposure and 30 percent at 1 year. Whether the apparent leveling off of the curve after 2 years of exposure implies that the risk of retinal toxicity becomes quite low at that time is not known with certainty. The number of subjects in this trial with more than 2 years of exposure was relatively small.

[Slide]

This slide summarizes the findings of the Toronto infantile spasms study. Infants, like adults, are susceptible to deleterious effects of vigabatrin on the retina. ERG can be used to monitor retinal function in infants and characterize the time course of the retinal abnormality associated with vigabatrin in this population.

As noted, the incidence and prevalence estimates for ERG abnormality in infants are somewhat higher than the rates of pVFD in adults, and the shortest duration of vigabatrin exposure at the time of observed onset of ERG abnormality is shorter than the time to onset of pVFD in adults. The reason for this difference may be higher vigabatrin dose used in infants, biological differences or technical differences.

[Slide]

Full-field ERG is an effective method for monitoring retinal function in infants. It has provided robust data characterizing the effects of vigabatrin used to treat infantile spasms on the retina. However, it requires sedation in most infants and anesthesia in some so it is not without risk. Moreover, outside the specialized centers the test is not readily available.

Unfortunately, some of these infants are severely impaired neurologically. Some, in fact, are cortically blind. For these infants visual testing, if it is invasive, is not clinically indicated. Hence, the monitoring of visual function during treatment for infantile spasms will need to be tailored to the individual patient.

Because of the risk of sedation and the lack of generally available ERG testing of infants, Ovation is not recommending ERG as a method for the routine monitoring of retinal function in infants treated with vigabatrin. Confrontation testing can be performed routinely and ERG used to investigate possible abnormalities when those results will affect clinical decision-making. Unfortunately, therapeutic options are quite limited for

many of these patients so for them vision testing will not affect clinical decisions.

[Slide]

The next special safety issue to be discussed is the occurrence of MRI T2 signal changes in some infants treated with vigabatrin for infantile spasms. Dr. Reid Patterson will introduce this issue by discussing the occurrence of intramyelinic edema and abnormal toxicology studies.

Intramyelinic Edema: Knowledge from Animal Studies

DR. PATTERSON: Good morning, ladies and gentlemen.

[Slide]

I am Reid Patterson. I am a preclinical development consultant for Ovation Pharmaceuticals.

[Slide]

The objectives of this presentation are to introduce you to the syndrome of intramyelinic edema; to briefly review research performed in IME associated with vigabatrin treatment in various animal models by the PhARMA sponsor; and to discuss the objectives, design and results of 2 rat studies, sponsored by Ovation, to define any unique safety risk to young children exposed to vigabatrin.

[Slide]

Intramyelinic edema, or IME, is defined as an accumulation of edema within the myelin sheath surrounding nerve fibers or axons. In the process of myelination oligodendrocytes deposit a lipid and protein coating or myelin sheath around major nerve fibers to enhance their speed of neural transmission and to protect the axonal processes.

The association of IME with vigabatrin was first discovered in the early 1980s when preclinical toxicology studies were conducted with vigabatrin. These changes developed within weeks of treatment in rats and dogs, appeared to stabilize rather than progress, and then disappeared upon drug withdrawal.

While discontinuation of dosing in dogs appeared to result in complete recovery, rats, especially after years of dosing, had minimal focal residual lesions of mineralization and/or swollen axons. Monkeys failed to develop evidence for IME despite vigabatrin and GABA concentrations comparable to or higher than that present in rats and dogs. Fortunately, imaging technologies, including magnetic resonance imaging or MRI, and several evoked

potential assays proved to be noninvasive methods for diagnosing the onset, monitoring recovery and confirming the absence of IME in animals and humans.

[Slide]

Since vigabatrin is proposed for use in young children with infantile spasms, Ovation recognized the need for the assessment of any adverse effects of treatment on the normal development during the pediatric period of life, and initiated a dialog with the FDA to design the most appropriate study.

The resulting rat study not only evaluated any adverse effects on reproductive, neurological, auditory and behavioral development but also included comprehensive assessments of any retinal and/or brain morphological changes as reported in older animals.

Dosing was conducted over 2 months from the neonatal age postnatal day 4, to a young adult age of 65 days. Functional and morphological data were obtained while these young rats were receiving vigabatrin and for almost 5 months after dosing was discontinued. Despite clear evidence for toxicity at the highest daily dosage and the presence of IME-like vacuolar brain lesions, there was no

evidence that vigabatrin interfered with pediatric development in this standard model.

[Slide]

All major regions of the brain were surveyed by light microscopy for evidence of pathology, with special emphasis on IME-like vacuolar changes, neural degeneration and gliosis. To assist in this process, the unique histochemical methods employed by neuropathologists were incorporated. An expert panel was assembled which concurred with the primary neuropathologist's interpretation of vacuolar changes.

[Slide]

While these vacuoles were morphologically consistent with IME, their close proximity to gray matter nuclei was inconsistent with lesion location in earlier reports from adult rats and in reports from IME-induced toxicity by other chemicals. However, the panel felt the apparent reversibility of these vacuolar changes was consistent with the recovery noted in the other models upon drug discontinuation.

They further confirmed the histologic and behavioral evidence for the absence of neurological

degeneration and gliosis. The panel recommended to Ovation that a further ultrastructural pathology study be conducted to define the specific cell affected, and to determine whether this vacuolation was consistent with earlier electron microscopic studies of IME.

[Slide]

Following the recommendation of the expert panel, Ovation commissioned study OVNC-9004, a study utilizing electron microscopy for higher resolution of these vacuolar brain changes. Most rats were again dosed from postnatal day 5 then euthanized after approximately 3, 6 or 9 weeks of vigabatrin exposure. Another group was not treated until postnatal day 12 and euthanized after only 2 weeks of treatment, designed to mimic an earlier study performed in adult rats.

Preliminary review of light microscopic sections indicated that the cerebellum nuclear region and adjacent white matter provided the most prominent and representative vacuolar lesions. Thus, this region was selected to provide ultrastructural characterization of these vacuoles and to explore for evidence of damage to the adjacent neutrophil, especially neurons and their axonal processes. Other

sections were not evaluated in detail as in the original study the distribution had already been established.

[Slide]

This slide will present photomicrographs from brain sections of rats treated with a maximum tolerated dose of vigabatrin. In the upper left-hand corner is a light microscopic overview, magnified 50 times, demonstrating small vacuoles in the cerebellar nuclear region.

With the magnification increased 125-fold, the right light micrograph depicts the same vacuoles surrounded by normal appearing neurons and neutrophil.

A different stain is used in the lower left light micrograph to further characterize the proximity of these vacuoles to normal appearing neurons.

In the electron photomicrograph in the right lower quadrant of this slide the tissue is magnified 12,500-fold to demonstrate the origin of the vacuole.

The blue arrow, to the left, points to the site of myelin splitting, with the external portion of myelin elevated away from the axon, denoted by the red arrow. The vacuole appears to be filled with a flocculent material of low electron density, consistent with reports of

intramyelinic edema fluid.

[Slide]

These light and ultrastructural pathology data confirm that these vacuoles were derived from splits and distentions of portions of myelin and surrounded myelinated axons, consistent with IME. While neither of these studies were designed to document any associated neuronal toxicity, they both provided no evidence for direct neuronal damage based on light microscopic histochemical methods used to detect neuronal damage and necrosis, and ultrastructural assessments to other neutrophil and neurons surrounding these distended myelin vacuoles.

Why these vacuolar changes were more consistently associated with gray matter in the younger rats than with the dense white matter tracks more commonly seen in older rats and other IME-induced lesions by other chemicals is unclear. However, all evidence suggests that these vacuoles behave like those at other sites as they resolve with drug removal and do not appear to result in permanent neurological damage.

[Slide]

In summary, vigabatrin associated IME in animals

is a reversible, non-progressive vacuolar change in myelin sheaths surrounding large nerve fibers. Vacuolar change in IME disappears with discontinuation of vigabatrin and don't appear to have any long-term developmental deficiencies or deficits in these rats. There is no evidence for loss of or damage to neurons, inflammation of gliosis associated with IME.

I thank you for your attention and am pleased to introduce Dr. Jim Wheless who will discuss the available human data on the association of vigabatrin treatment and subsequent MRI abnormalities.

Clinical MRI Abnormalities

DR. WHELESS: Good morning.

[Slide]

I am Jim Wheless. I am Professor and Chief of Pediatric Neurology at the University of Tennessee Health Science Center, Director of the Neuroscience Institute and LeBonheur Comprehensive Epilepsy Program at LeBonheur Children's Medical Center, and Clinical Chief and Director of Pediatric Neurology at St. Jude Children's Research Hospital.

Today I am going to review what is currently known

about vigabatrin and MRI abnormalities when this medication is used to treat infantile spasms. Let's begin with a quick historical review of what we know about imaging and the use of this drug.

[Slide]

Reid Patterson has just reviewed the preclinical toxicology of vigabatrin. I will now review the clinical experience with this drug as it relates to MRI abnormalities. As you heard yesterday, prior prospective clinical trials using vigabatrin in treating adults and children with intractable complex partial seizures incorporated serial MRIs into study design and showed no evidence of MRI changes associated with vigabatrin use.

Additionally, vigabatrin is approved in Europe, Canada and many other countries, and there have been no reports of MRI changes after approval in these countries with nearly 20 years of clinical use.

However, recent data have come to light indicating that the use of vigabatrin to treat infantile spasms may be associated with transient MRI abnormalities. These are characterized by a hyper-intense T2 signal within deep brain structures. Today I will review what is currently known

about vigabatrin and MRI abnormalities when this medication is used to treat infantile spasms.

[Slide]

At the 2006 American Epilepsy Society meeting Dr. Phillip Pearl, from the National Children's Medical Center in Washington, DC, reported a series of 15 children from his institution. These infants were treated with vigabatrin predominantly for infantile spasms. Within this case series he found 3 patients who had a distinctive pattern of unexplained MRI abnormalities. This involved increase in T2 signal, seen predominantly in the basal ganglia and brain stem.

Although this report had the limitations of a case series, such as that the causal relationship could not be established for vigabatrin as these infants had been treated with multiple pharmacologic and non-pharmacologic therapies, this finding did renew a concern related to this issue.

As a result of this report, additional studies were initiated by Ovation to better characterize the association between vigabatrin use in infantile spasms and MRI abnormalities. I will review these studies after showing you a typical MRI scan with the abnormalities

associated with vigabatrin use.

[Slide]

This series of images shows the typical MRI abnormalities involving the deep gray matter. On the top you see the images of a single infant. The first one is before treatment with vigabatrin as part of the diagnostic evaluation. The second scan was obtained later during the course of infantile spasms, showing normal myelination and maturation with age, but the arrow also highlights the subtle increased signal seen on T2 MRI in the thalami. Of note, as you can see in the images below, this abnormality is much easier to appreciate using diffusion weighted images where the abnormality is much more distinct.

It is also notable that DWI imaging was not routinely performed as part of the evaluation of children with epilepsy prior to the last 3 or 4 years. The DWI sequences show changes in water movement and, as such, are more likely to show changes related to restriction of water movement or edema.

[Slide]

Pearl’s reports led to further investigation of the possible link between the use of vigabatrin for

infantile spasms and the occurrence of MRI abnormalities. At first Ovation reviewed the postmarketing reports of MRI abnormalities and simultaneously initiated study OV-1019 for the vigabatrin-naive and vigabatrin population. I now will discuss the results of these studies.

[Slide]

Ovation reviewed the available phase 4 postmarketing safety concerns reported in infants, especially those that reported MRI abnormalities. This specific report went back to the first use of vigabatrin infants, not the last 10 years as Dr. Sagar just showed you with the overall phase 4 reports. Twenty were noted to have MRI abnormalities. Three of the 20 children had transient motor symptoms on exam. When the drug was discontinued the motor symptoms resolved. The underlying cause could not be determined from this type of data.

While Ovation was performing this review, a protocol was developed to assess the MRI in children with MRI abnormalities and I will discuss this next.

[Slide]

The goal of the present retrospective, multicenter study was to test the hypothesis that vigabatrin is

associated with transient MRI abnormalities in infants with infantile spasms, and to estimate this prevalence against the background of MRI abnormalities known to occur in infants with epilepsy. My center was one of 11 and the largest contributor to this study.

The study was initiated at each site after IRB approval was obtained. The eligibility criteria were that children had infantile spasms; they were less than age 25 months at diagnosis; they had MRIs available for evaluation including at least one with T2-weighted and flair or DWI sequences performed after the infantile spasms diagnosis; and before age 36 months, and they were treated either with vigabatrin or another medication.

The primary aim was to compare the prespecified MRI abnormalities between vigabatrin-exposed and vigabatrin-naive cohorts. The secondary aim was to compare risk factors for these abnormalities.

The images were reviewed in a blinded fashion by two independent neuroradiologists, with a third senior radiologist adjudicating if needed. Researchers were asked to report the MRI abnormalities and categorize the MRIs as either normal, as abnormal due to a well-categorized process

such as tuberous sclerosis complex or abnormal and non-explained by a well-categorized pathologic process. These were the prespecified abnormalities the studies sought.

[Slide]

Data were collected on vigabatrin exposure that included duration, daily dose and cumulative dose. Vigabatrin-naive patients were on other therapies for infantile spasms.

[Slide]

Prevalence was defined as the occurrence of at least one prespecified abnormality, single abnormality on MRI and T2 flair and/or DWI imaging during the treatment period. A baseline scan was not required. The prevalence population included all subjects who had a determinant MRI examination during or after treatment with vigabatrin.

As you see, the abnormality was seen in 4 of 35 children in the low dose group; 13 of the 62 children in the high dose group; and 4 of 101 children in the vigabatrin-naive group. There were 3 patients in whom we were unable to determine the dose from their records. The relative risk is shown for all vigabatrin doses versus vigabatrin-naive patients.

[Slide]

Incidence population required a baseline MRI that had to be free of the prespecified abnormalities and at least one post-baseline MRI. The purpose of analyzing the incidence population was to capture all cases with MRI change from normal to abnormal.

In the low dose group 4 of 12 children had the MRI abnormality; in the high dose group 6 of 16 children had the MRI abnormality; and in the vigabatrin-naive group 1 of 17 children had the MRI abnormality. The relative risk, again, is shown for all vigabatrin dose groups versus vigabatrin naive.

[Slide]

So, a total of 101 children received vigabatrin as either initial or subsequent therapy for treatment of infantile spasms. Twenty-one of these had the prespecified abnormality seen on MRI while on vigabatrin, of which 12 had at least 1 subsequent determinant MRI evaluation. Of these 12, 4 continued on vigabatrin, 3 having resolution of MRI findings while on therapy. The other 8 patients discontinued vigabatrin, with resolution of the MRI findings in 15 percent of the patients. In total, 7 of the 12 had

resolution of the MRI abnormality.

[Slide]

Let me now show you a series of images from a patient who had MRI abnormalities that resolved. The MRIs on the left, both top and bottom, are prior to treatment with vigabatrin. This is a male infant with Down's syndrome. In the middle panel are his images after 4 months of treatment with vigabatrin. Again, you see the subtle increase in signal in the thalamus, seen bilaterally on T2 images and much more distinctly on DWI images. The right panel shows resolution of these abnormalities on MRI images obtained 3.5 months after vigabatrin discontinuation.

[Slide]

In summary, when vigabatrin-associated abnormalities were seen on MRI they had a characteristic location and appearance. They are typically seen in the basal ganglia or brain stem. There is an elevated prevalence with higher doses. A seemingly dose-dependent relationship is possible but not proven. In many patients these abnormalities were resolved on subsequent MRIs and there were no reports of clinical sequelae.

[Slide]

While the data from this study was being analyzed two subsequent manuscripts were published, one in the U.S. and one in Europe. There were similar MRI abnormalities noted in both publications, and all but one patient had resolution of the MRI abnormalities with discontinuation of vigabatrin, supporting the findings of our study.

[Slide]

So, what can we conclude from all of this data about the use of vigabatrin to treat infantile spasms? I believe there are three conclusions: First, vigabatrin exposure is associated with the increased incidence and prevalence of MRI abnormalities in this age group and condition.

Second, there is seemingly a dose-dependent relationship between vigabatrin use and the MRI abnormalities. Finally, the majority of these MRI abnormalities were reversible both after discontinuing drug or if the child remained on vigabatrin therapy.

Thank you for your attention. Tim Cunniff will now present the proposed Ovation risk management strategy.

Ovation Risk Management Strategy

DR. CUNNIFF: Since we have a few new attendees

today I want to briefly run through this. I won't give the full presentation from yesterday though.

[Slide]

Ovation will provide a comprehensive risk evaluation and mitigation plan, or REMS, that will accompany the approval of Sabril to ensure that the drug is used safely by appropriate patients.

I do want to remind the committee that many risk management tools will be incorporated into our REMS, including informative labeling, communication and education programs, and several restrictive elements to ensure safe use, including a mandatory registry. It is important to note that patients currently being treated with imported drug from other countries in the U.S. are now receiving Sabril without any of these safeguards.

With respect to labeling, the MRI abnormalities just discussed by Dr. Wheless will be summarized as a warning statement in both the physician package insert and the patient medication guide. Guidance will also be provided to physicians as to appropriate circumstances in which to consider MRI monitoring. Our communication plan will focus on physician and patient caregiver education

through a variety of mechanisms, as discussed yesterday.

[Slide]

We will also use many restrictive elements to ensure the safe use of Sabril in patients with infantile spasms throughout the prescribing, dispensing and treatment phases. The initial prescription for Sabril can only be written by board-certified neurologists.

In order to prescribe Sabril, a physician first must undergo education and, after completing this education, must attest to having experience in treating epilepsy and having an understanding of Sabril's approved clinical indications, the risk, and recommendations for visual testing. Following this attestation, the physician is registered and then can only prescribe Sabril evaluation phase treatment. The drug will only be dispensed if all requirements for physician and patient registration are satisfied.

Before a patient can receive maintenance phase treatment, a mandatory benefit/risk assessment must be performed to ensure that patients without clinically meaningful improvement in spasm control are discontinued from therapy. Sabril dispensing will be limited to a few

select specialty pharmacies comprising a controlled distribution system.

A visual testing reminder system will be available to help patients complete regular ophthalmologic testing, and results from this testing will be collected. All patients will also participate in a mandatory Sabril registry, and data from this registry will be reviewed, analyzed and submitted to the FDA on an annual basis.

I would now like to invite Dr. Jack Pellock to the podium to conclude our presentation with a benefit/risk assessment.

Benefit/Risk Assessment

DR. PELLOCK: Thank you, Jim. Good morning.

[Slide]

My name is Jack Pellock. I am Professor and Chair of Child Neurology at Virginia Commonwealth University, down the road in Richmond. I am here to discuss the benefit/risk assessment of infantile spasms treatment with vigabatrin.

[Slide]

Dr. Shields has already pointed out that uncontrolled infantile spasms have serious consequences. In children whose spasms are not controlled the spasms

generally evolve to other seizure types within 1-2 years. In fact, 50-70 percent of these patients develop other seizure types, usually catastrophic about 50 percent.

This is a life-threatening disorder. The mortality rate, depending upon the study, may be up to 30 percent. Of those, about one-third occur in the first 2 years of life. There are other catastrophic problems. Of the survivors, 20-30-year follow up would show us that 10-30 percent only will be normal, whereas the others will have other difficulties, both intellectual and motor difficulties. A third will develop autism.

Thus, this is a rare but devastating child neurology emergency, emergency to the child, to the parents, to the child neurologist and, in fact, the entire family.

[Slide]

So, where are we today in treating children with infantile spasms? As Dr. Shields noted, there are no FDA-approved treatments in the United States for treating this catastrophic disorder. The current standard of care includes off-label treatment with ACTH or corticosteroids which are associated with significant safety issues, adverse events of infection and potentially life-threatening

hypertension, especially with prolonged use. ACTH and corticosteroid use is limited by tolerability issues and relapse rates are not rare.

However, early effective treatment is important for favorable developmental outcomes for infantile spasms patients. A delay in spasm cessation, as you have heard, has been associated with poor developmental outcomes. Vigabatrin meets this unmet need for infantile spasms treatment even in patients who have been previously treated with other agents.

The benefit/risk assessment I will discuss favors aggressive therapy, and the risks with this treatment are manageable. Remember, these children are seen very frequently and followed very closely throughout their diagnosis and subsequent follow up by the child neurologist or other physicians.

[Slide]

As Dr. Sagar reviewed, vigabatrin treatment is associated with significant improvement of spasm cessation. There is a high response rate across multiple infantile spasms etiologies. The response rate is complete cessation of spasms and normalization of the EEG. This is very

different than other types of epilepsy-Bcomplete cessation of spasms and normalization of EEG. There is rapid onset of spasm cessation, typically in 2-4 weeks of treatment, and it is generally well tolerated with vigabatrin. For those who respond, there has been a demonstrated improvement in cognitive outcomes. Vigabatrin has been accepted as first-line clinical therapy around the world, including treatment guidelines proposed in the United States.

[Slide]

There are associated risks. These include, as you have heard, peripheral visual field defects. These are challenging to measure in infants but can be monitored by ERG or confrontation testing which are recommended to be performed by physicians at regular intervals. The electrophysiologic test can demonstrate retinal effects underlying the pVFD but, of course, these may require sedating a very young infant to do so. About 3-5 percent of children treated with vigabatrin may develop ERG correlates of pVFD. The earliest confirmed ERG abnormality has occurred at 3 months.

As you have just heard, presence of T2 abnormalities have been detected on MRI in retrospect and

case reports from the literature. However, these changes generally resolve with discontinuation or reduction of the vigabatrin dose. There is no histologic confirmation of intramyelinic edema in humans.

Despite this finding, routine MRI surveillance requiring sedation is not recommended. There is a small but definite risk of sedation to perform the MRI. If abnormalities are detected physicians must balance the benefit of vigabatrin therapy versus the risk of MRI surveillance. In managing these risks non-responders can be discontinued and early responders are evaluated frequently by clinical assessment.

[Slide]

Let’s quickly analyze the timeline to evaluate the efficacy in IS patients. First, once the patient is appropriately diagnosed with infantile spasms the physician can rapidly begin treatment and assessment, as was discussed by Dr. Shields.

As you remember, most patients will respond in 2-4 weeks but there will be others that take more time to fully respond depending upon their etiologies. This gives us an opportunity to evaluate the patients to consider whether or

not they should continue the therapy or whether it has been unsuccessful and they should be withdrawn.

The earliest confirmed electrophysiologic changes, as we have noted, are at approximately 3 months. Therefore, we have a period of time where we can perform the recommended ongoing ophthalmologic testing, patient assessment and treatment to see if, in fact, the benefit/risk profile for the patient provides a case that treatment should or should not be continued.

[Slide]

The benefit to risk assessment is positive. The substantial benefits of treatment with vigabatrin outweigh the risk in patients who respond. Infantile spasms are a true neurologic emergency. As I said before, the patients, the family, the mothers, the fathers, the sisters, the brothersB-it affects everyone and it affects the physicians who treat them.

There are currently no approved therapies in the U.S. Today, however, you have seen that treatment with vigabatrin has produced spasm cessation in multiple studies across all IS etiologies. Vigabatrin is recognized internationally and within the U.S. in treatment guidelines

as effective monotherapy for the treatment of infantile spasms, both cryptogenic, symptomatic, including tuberous sclerosis.

The risks of MRI abnormalities and the peripheral VFD can be effectively managed in these patients with vigabatrin. For infants who respond to vigabatrin the benefit of spasm cessation exceeds the risks of peripheral visual field defects and MRI changes. But, recall, as opposed to older patients with epilepsy, these patients are followed very frequently, with very careful examinations by child neurologists. We do visual screening every time. We do motor examinations every time.

[Slide]

In summary, vigabatrin is recognized as first-line therapy worldwide for infantile spasms, West syndrome. Currently, there is no regulated drug available to infants requiring treatment in the United States. These infants are now receiving vigabatrin without proper safety instructions. The proposed REMS will provide these safeguards, education and instructions. Children with infantile spasms and the neurologists need vigabatrin as a therapeutic option now.

I will now turn the podium over to Dr. Tim Cunniff

who will answer any clarifying questions.

Clarifying Questions

DR. GOLDSTEIN: Thank you. For the committee, again, we have about ten minutes or so for focused clarifying questions. Remember, the afternoon session will have more than ample time, I hope, to discuss each one of the issues. Again, just as a general reminder, what I will do is I will try to take questions from people who haven't asked them first and then we will go around for seconds and thirds. Dr. Katz, you wanted to make a comment?

DR. KATZ: Well, I had a question. I don't know if I am first on the list.

DR. GOLDSTEIN: Go ahead.

DR. KATZ: I think it was Dr. Sagar's slide 42 which refers to the ERG results in the Toronto study. The percentage of patients with abnormalities, as displayed here, seems to sort of level off and it goes out to 72 months. But do you have a Kaplan-Meier curve of this, or can you tell us how many patients were actually followed beyond, let's say, 24 months?

DR. SAGAR: Beyond 24 months it is a relatively small number of patients. I can't give you the exact number

but it is less than 10.

DR. KATZ: And you start out with how many patients here?

DR. SAGAR: I have to look at the exact number.

DR. KATZ: Okay. There is sort of a perception from this slide--

DR. SAGAR: We start out with 70, I am sorry.

DR. KATZ: Seventy. So, there is sort of a perception from this slide I think that we have a lot of long-term data but that is probably not true. Is that right?

DR. SAGAR: Yes, I tried to make that point. We don't have long-term data and I don't think any conclusions can be drawn about the apparent leveling off of this curve after 24 months. I think the number of patients and the data is reasonable up to about 24 months but I wouldn't draw any conclusions after that point. I agree with you entirely, Dr. Katz.

DR. GOLDSTEIN: Dr. Hirtz?

DR. HIRTZ: I have a question for Dr. Pellock and others. I am a little confused about whether Ovation is recommending vigabatrin as first-line therapy. I have no

question about its value and efficacy, but I am not sure about the issue of first-line versus ACTH. The data from the U.K. study, particularly the newer data that is available that was published in 2005, with the long-term follow up showed that the outcome at 14 months was equal between the two overall, but for the children with no known etiology, so excluding the TS patients, there was a statistically significantly better outcome with ACTH.

So, I would like to hear a little bit more about your feeling about ACTH versus vigabatrin and what you are actually proposing.

DR. PELLOCK: As you know, Dr. Hirtz, tuberous sclerosis was excluded from that study, which may have changed the numbers, and at the 14-month follow up there was a very slight difference in developmental outcome. There is an abstract that suggests there might be wider separation as years go on. But, as you know, those studies did not do all EEGs and there were other difficulties.

I think it is very hard, on the basis of that study, to say that it is absolutely one or another. As people have said this morning, does tuberous sclerosis deserve as number one vigabatrin? Do other etiologies

deserve ACTH as number one? I don't think we have that data today. So, I would be in favor, and I think it is being proposed, that they are firstB-well, this is first-line therapy.

DR. GOLDSTEIN: Dr. Repka?

DR. REPKA: Thank you. Mike Repka. I have a couple of questions. If you could put that other image back of the cumulative prevalence plot? In the preliminary data you mention that, in fact, the ERG abnormalities in the control population could be as high as 38 percent, yet this plot started at zero.

DR. SAGAR: That plot is a plot of incidence so those are the subset of subjects that had a normal baseline exam and then developed an abnormality during treatment.

DR. REPKA: Thank you for that clarification. The second question, and I am not sure to whom, one of the things that struck me about this drug in the infant population was the recognition by the Toronto group about five years ago of an optic neuropathy associated with the use of this drug in children, not something that I am aware of that has been reported particularly in adults.

I noticed it is not in either your background

document or in the presentation today, and I wondered if that is because the Toronto group is not standing behind that finding anymore. The reference is in your document but there is no discussion that I could find.

DR. SAGAR: I can ask Dr. Westall, from the Toronto group, if she can comment on that.

DR. REPKA: Thanks.

DR. SAGAR: This is Dr. Carol Westall. She is a Ph.D. vision scientist, not a clinician.

DR. WESTALL: Carol Westall, Hospital for Sick Children, Toronto. In answer to your question, that report was a case report of three children. As such in a case report--I can remember the cases. I can remember the 10-year old. I can remember she has normal visual acuity, normal color vision, normal ERG, normal BEP, and had a retinal defect and, when measured for visual defect, this 10-year old did have a visual field defect. So, is a case report and I certainly don't put as much emphasis on that report as I do on some of my other work which has 200 infants in it.

DR. GOLDSTEIN: Dr. Gorman?

DR. GORMAN: My question is for Dr. Sagar. Would

you care to speculate on the stunning difference in efficacy between the FR03 group and the other studies that you cited in the tuberous sclerosis group with basically 100 percent efficacy in that group and only 30-50 percent efficacy in the other tuberous sclerosis studies?

DR. SAGAR: In general, in the literature the effectiveness of vigabatrin, that varies between about--initial therapy of tuberous sclerosis varies between about 80 percent and upwards. I thinkB-and I will ask maybe Dr. Pellock to comment on thisB-I think the appearance of both conditions has been that it is not 100 percent effective in tuberous sclerosis but has a high efficacy rate.

DR. GORMAN: Would you consider then that it was the choice of endpoints, which was one month as opposed to a much shorter time frame; the choice of dose, which was higher in the French study than in the other study; or the adequacy of the French medical system in identifying tuberous sclerosis and its associated specific seizure patterns? Because you have made the emphasis that the time from diagnosis to treatment affects both the efficacy and the long-term outcome.

DR. SAGAR: I can’t comment on the French medical

system and the product with particular investigators who carried out the study led by Drs. Kaplan and Gerome who were quite expert in pediatric neurology. This one difference is that that study did not achieve confirmation. That might be one important difference between the other studies.

DR. PELLOCK: Just very quickly--

DR. GOLDSTEIN: Please, when you are answering say your name for the recorder.

DR. PELLOCK: Jack Pellock. Commenting on infantile spasms studies in general, if one looks upon old literature you will see 100 percent in one study with the same agent, seemingly given the same way, and you will see 30 percent in another study. I think it is partially sampling error and, again, what stringent criteria were put in force. Was it EEG controlled; was it not EEG controlled? What day did they do their validity or their emphasis upon seizure freedom? Was it long-term or only clinical?

So, there are a lot of variations. But no matter what agent we looked at when you see numbers of studies you see this variability. I would contend that none of our agents, unfortunately, are 100 percent.

DR. GOLDSTEIN: Dr. Katz, Dr. Vega, Dr. Twyman and

then a break. Dr. Temple too I guess.

DR. KATZ: Just one clarification. I think study FR03 was unblinded so people knew what treatment assignment the patients were on. So, that certainly has the potential to affect the outcome.

I had a question also on study 1A, maybe slide 8. Here, by the protocol as specified, this was the study in which you had to have an EEG within 3 days at the end of the 7-day seizure-free period and the p value by the analysis presented hereB-and we will talk more about this when Dr. Sheridan does, but it was 0.037. But when you did an EEG at any time it was much lower. I think you did EEGs out to 21 days after the end, I think you said.

Can you say anything about what the patients were doing clinically during that extended period of time? Were they spasm free, or what do we know?

DR. SAGAR: Yes, all these subjects remained spasm free to the time of the video EEG.

DR. GOLDSTEIN: Dr. Vega?

DR. VEGA: My question is regarding the initial treatment, the duration of the therapy as seen in slide CUI-10. It was said that the duration of the therapy is 3-12

months until age 1 year. I was confused about that because, I mean, I know a lot of older children are taking this medication. Can you clarify that?

DR. SAGAR: I will ask Dr. Shields to comment on that.

DR. SHIELDS: Fortunately, duration of therapy is evolving as our understanding of the issues happens here. Many of our patients actually went out to 3 years, which is the limit that we had when we designed what is called the 1A study and many patients have gone that long.

I don't think I would leave a patient on for 3 years at this point. My view is that the risk of infantile spasms begins to decline at about 1 year of age and I want to try to take the patients off. So, my role at this point or my plan at this point is that when a patient gets to 3 years and is spasm free I try to take them off the medication. [Inaudible]. If they don't have spasms, then they are off.

DR. VEGA: Is that true for all children, the TS, the symptomatic, the cryptogenic, I mean for all the groups?

DR. SHIELDS: In general, yes. The TS patients may be a little bit different because partial seizures and that

group of patients may respond well to vigabatrin. So, that is a little different calculus that goes on with those patients.

DR. GOLDSTEIN: While you are there, just one other question. The 1A study, was that blind or unblind, those assessments?

DR. SHIELDS: It was single-blind. We did not have a placebo. This was a big debate we had with the agency because we were just planning to do a compassionate-use study and we just wanted the drug to be able to treat our patients. I could go through the whole history but I don't think I need to. But they wanted a placebo-controlled study and we could not do that. We had drug. Aventis gave us pills and a little bit of money to monitor and be able to do a data analysis, and we worked out the high dose and the low dose, and for the low dose the smallest we could go was a quarter of the pill. So, that kind of defined what low dose was going to be.

DR. GOLDSTEIN: Dr. Twyman?

DR. TWYMAN: My question actually was related to the duration also but, in addition to that, are there any data available on children, since they have been treated

since 1989, with regard to visual fields when they have been exposed to vigabatrin as an infant?

DR. SAGAR: There is very limited data. Ovation is supporting a study to be carried out by the Paris group who are going to bring back children who are over 10 years of age who were exposed to vigabatrin as infants to have visual field testing.

There is a small study from Boston, performed by Dr. Ann Fulton. This is as yet unpublished. She provided us with a preprint of her manuscript. In her study she was able to examine 28 children using a special perimetry technique that could be applied to young children down to the age of about 2. She brought back children who had been exposed to vigabatrin to test with the special perimetry technique, and 8 of 28 of them had visual field deficits by this measure.

The children who were older, who could do both Goldman and this special type of perimetry, the visual fields were comparable. So, she thinks this is a reliable method that can be used in younger children, but it has not been validated in a large subset yet. Her numbers were 8 of 28 who had a peripheral visual field defect. There is not a

lot of data.

DR. GOLDSTEIN: Thanks. Unfortunately, we have to kind of stay right on schedule today and it is going to be logistically impossible for everybody to get through the bathroom line and back at a quarter of. So, we will start maybe a couple of minutes after that. Folks who are listed for questions that we didn't have time to get to now, we will do you first after the FDA presentations so we will be able to get caught up. So, plan on taking maybe an 8-minute break and then we will be back.

[Brief recess]

FDA Presentation

Ophthalmic Findings in Pediatrics

DR. FARKAS: Good morning.

[[Slide]

I am Ron Farkas, from the Division of Neurology Products at FDA. Today's talk is about ophthalmic findings in pediatrics and particularly in infantile spasms.

[Slide]

This is just to review FDA concerns in adults that were talked about in detail yesterday. Vigabatrin is thought to cause visual field constriction. FDA believes

that in adults the onset and progression is variable and unpredictable and that one-third or more of patients are affected after several years, with about an equal proportion being affected with mild, moderate or severe field constriction. FDA is concerned that damage to central vision may occur and believe that it is uncertain if damage can worsen after stopping drug.

[Slide]

FDA's interpretation of the data is that the peak incidence of visual damage occurs at about 1 years, that onset within a few weeks or months is not rare, and that no safe exposure is known where visual damage does not occur.

Of course, after reviewing that data in adults, FDA wants to stress that it is uncertain just from adults if these same findings would occur in infants and in infantile spasms.

[Slide]

Now to talk about infantile spasms--

[Slide]

On physical exam in the peripheral retina of children with infantile spasms there is gross retinal atrophy and granular appearance which would seemingly

correlate with a visual field defect. In the central retina there is more subtle atrophy and wrinkling in some patients, which may indicate, in FDA's interpretation, damage that might risk central acuity. So, these observations from physical exam did seem qualitatively similar to findings in adults.

[Slide]

As was mentioned, perimetry for visual field testing is not possible in infants and electroretinography has been the most studied objective method to detect retinal injury from vigabatrin in infants. There is little data available for other objective methods.

[Slide]

When FDA tries to think about how ERG would be used in children with infantile spasms, we try to think are the ERG results true. That is the first question. If the result is normal, is damage absent? If the result is abnormal, is damage present? Basically, this is just like an analysis for any test. What is the sensitivity; what is the specificity; positive predictive value, etc.

The second question that FDA asks is, is the test result clinically useful? In this case, can it help prevent

damage, or can it only diagnose damage once irreversible damage has occurred?

[Slide]

Importantly, in this situation ERG performance as a clinical monitoring test has not meaningfully been addressed in the submission to the FDA, or FDA did not find that also in the literature. Importantly, there is, FDA believes, a correlation between ERG and vigabatrin retinal damage but a correlation itself can exist without being strong enough to make a reliable or useful clinical test.

[Slide]

So, the FDA attempted to look through the literature and the data that was submitted to try to assess the performance of ERG in finding retinal damage from vigabatrin. But there was very little of the key data that is necessary to do that kind of analysis.

For example, in order to know if a test is identifying patients who have an abnormality you have to know that the patient actually has the abnormality. To know that, you would have to have information from some other method. Likewise, you have to know that a patient that is identified as normal by ERG has no damage confirmed by some

other method.

[Slide]

Most of the data, as was pointed out by the sponsor, on ERG and infantile spasms is from the Toronto study, which is a leading center for pediatric ERG and has a large experience with vigabatrin and infantile spasms.

[Slide]

The prospective arm of that study included 117 patients with greater than or equal to one post-baseline exam. There was also a retrospective arm including 89 patients with at least one exam but no baseline exam.

[Slide]

The age at the most recent ERG in the Toronto study was about 2 years. The average patient was examined 2-3 times over 6-12 months. And, about 80 percent of patients were followed up for 2 years or less.

I think that this point came up in the questions to the sponsor's presentation in that there really isn't data going out past on average 12 months, and then for 80 percent of patients 2 years. So, there isn't experience with ERG past that point.

[Slide]

This is the type of data that is available for the infantile spasms patients. One important point is that the results for ERG are in microvolts and the clinical entity that is being diagnosed is visual field defect or retinal damage. And, there is no clear correlation between microvolts and visual field defect. There is some correlation but there is no clear correlation.

So, if it is 100 microvolts, it seems that is normal and as the microvolts get lower that is worrisome. But FDA doesn't have any information about if 25 microvolts correlates to mild visual field defect or maybe 50 microvolts, or if 25 microvolts is severe field defect. So, that information isn't available.

Just also to explain the figure, these asterisks are the sponsor's interpretation of abnormal fields, and both eyes were not tested at each session. So, red dots are left eye and green dots are right eye.

[Slide]

Then FDA was faced with the task of trying to interpret the clinical meaning of these tests, and one way that we tried to approach it was as a physician would approach it who was doing one of these tests to monitor a

patient on vigabatrin. So, in fact, the physician would be looking at the first test. Here it was done at about 4 months, and then he would do another test and another test. So, at each test a decision would have to be made if the patient should be kept on vigabatrin or not.

[Slide]

So, for this example the tests are increasing and there really isn't any indication that there is a problem. Then, between 1.5 years and 2 years there is a very large, about 85 percent, decrease in the ERG. So, the question is what is happening?

Well, one interpretation is that this represents an 85 percent decrease in retinal function and perhaps retinal damage. But, as I noted before, the FDA doesn't have the information that would be necessary to determine if the test is accurate. So, we are not sure if this really represents vigabatrin damage.

[Slide]

When we look through all the data that was available to us we saw a variation in the ERG data from test to test that we were unable to explain in terms of the presence or the absence of a visual field defect. While I

have drawn black lines over this data, which perhaps exaggerates the variability, what we saw is that with some of the ERGs the ERG went up, went down. In some it stayed constant. It went down; it went up, etc., maybe down, then up. So, we couldn't discern signal from noise in the ERG data.

[Slide]

The sponsor concluded from this data that 54 percent of patients with a normal baseline, so that was excluding 38 percent of patientsB-that 54 percent of the patients with a normal baseline changed to abnormal on one or more subsequent tests.

The sponsor realized that it was uncertain if that represented true positive findings. So, they adopted sustained abnormality on the final 2 exams as the confirmation of a true abnormality. The problem with that is that it doesn't really address how much change is due to test variability.

So, if in that first test, where there is 54 percent of patients with an abnormality, if there is a high chance of a false positive, then on 2 tests there is a little bit less chance of both being false positives but

there is still a pretty good chance of both tests being false positives. Then it would be thought incorrectly that the patient would have a visual field defect and vigabatrin might be stopped when that would be inappropriate.

The analogy is very simple, just similar to a coin toss. If a coin comes up once heads, maybe it is heads on both sides. If it comes up twice heads, you have a little more concern that the coin is heads on both sides. But only if you toss that coin a lot of times could you be certain that it was a trick coin and it was heads all the time.

Another concern that I didn't draw in detail here is that we are talking about serial testing. So, if there is a rate of false positives the more that you test, the more likely it is that you will hit false positives, even 2 false positives in a row.

[Slide]

The FDA is also concerned about conclusions based on what we consider biased endpoints. So, the sponsor had spoken about the first ERG abnormality being identified at 3 months. Well, in fact, the first post-baseline exam for most patients was at 6 months. It is true that some patients later in the study had ERG exams at 3 months but

certainly no significant number of patients had an ERG exam before 3 months. So, it simply would not be possible to find an abnormality that wasn't looked for before 3 months. It was not looked for.

Also, the definition of a confirmed abnormality or a sustained abnormality is based on 2 abnormal tests. If the second test is at 1 year, then by definition a patient is never confirmed to be abnormal until 1 year. But that is an artifact of when the test is given. It doesn't tell you when the abnormality actually occurred.

[Slide]

To go back to the issue of the patients that are abnormal at baseline, it is unclear to FDA how this 38 percent of patients should be monitored because, certainly, if they start out below normal then you could not use a change to abnormality as an indication of an abnormality. I should point out that this normal line, here, is not adjusted for age. It would curve upwards.

[Slide]

So, I have been talking mainly about what you might call specificity, about false positives, but I haven't been talking very much about sensitivity, which is the

question of how many patients with an abnormality is the ERG test missing?

While both sensitivity and specificity really need to be referred to some other method for confirmation, in particular there isn't really a way to get at sensitivity without comparing to some other method. So, the proportion of patients detected is not informative about the number of patients that are missed.

One way to approach this question, of course, as has been mentioned, is to find patients that have had both an ERG and that have had perimetry. The data that FDA has is not in infantile spasms patients. We just heard that apparently there is some data being developed about infantile spasms patients who have had ERG and perimetry but it seems that isn't currently available.

[Slide]

So, to go back to data that we do have correlating ERG and visual field defect in adult patients, I talked about the study yesterday, study R003, a prospective study in adult patients with complex partial seizures. There were 25 patients enrolled and 7 patients, or 28 percent, developed a field defect, 4 of mild severity and 3 of

moderate severity at first diagnosis.

[Slide]

ERG was done in those patients and did not identify a field defect in any of the 4 patients with mild damage and only identified an abnormality in 1 of 3 patients with moderate damage. So, there is a concern that the sensitivity of ERG for vigabatrin retinal damage is low.

[Slide]

This is also a case that was mentioned yesterday and briefly today by Dr. Westall. This is a 10-year old girl with complex partial seizures, examined in Toronto. She was on vigabatrin for 4 years. She had a severe visual field constriction. The girl's visual field is this black line and the normal is the red, dotted line. So, again, this raises concern that a patient can have a visual field defect, even a severe field constriction, while still having a normal ERG.

[Slide]

This slide is just a diagram of what possibly might be going on with a patient's vision over time when they are on vigabatrin. At the beginning potentially there is a period of time where the visual field defect isn't

developing. We don't really know that though, I should say. It might be developing right away. But just for this diagram, maybe there is a period where visual field defect doesn't develop and then at some point it does develop.

The question is, is the vision test detecting damage that has already occurred irreversibly, or is it giving information that can be used to prevent damage?

[Slide]

What it really hinges on is how well, how closely, how accurately the vision can be followed over time. In this case, and, again, this is just FDA's estimate, if the ERG test has some noise in it or has a significant amount of noise in it when the vision does decrease the ERG can show that the vision has decreased. But by the time that there is that certainty, by the time that the ERG test has been repeated and the result is confirmed the damage has been detected but not prevented.

[Slide]

Then there is, of course, the important question of what is the clinical consequence of vigabatrin visual damage in infants with infantile spasms?

[Slide]

There is very limited data addressing this, really just case reports. One concern of FDA is that in adults the damage or the effect of the damage can relate to the ability to use compensatory strategies like visual scanning. But the FDA is not aware of data in infantile spasms patients that would address their ability to compensate, functionally compensate for their vision loss.

[Slide]

Again, what we do have is a small number of case reports, again from the Toronto study, that raise concern about the functional effect of vision loss in patients with infantile spasms.

This case is a 2.5-year old boy with trisomy 21 with infantile spasms since 9 months of age. After 24 months on vigabatrin the fundus exam showed retinal atrophy involving most of the retina, and the paper stressed relatively less involvement of the macula, and the macula showed wrinkling and irregular thickness. The ERG was about 50 percent below expected, and this was attributed by the investigator, as far as FDA can tell, to vigabatrin.

[Slide]

The acuity in this patient was in the lower half

of age-expected normal, and in the clinic the patient did not respond to objects in the periphery and was noted to stare straight ahead during testing. The parents of the patient reported that he stared straight ahead at home; responded more to sound than visual cues; and the parent reported that they had to attract his attention downward to his food at mealtimes by tapping on his plate.

I want to stress that FDA certainly does not know that this behavior was due to vigabatrin visual damage, but our interpretation of the case report is that the investigator believed that this might represent a functional consequence of vigabatrin visual damage.

[Slide]

The conclusions of FDA are that vigabatrin can damage the peripheral and central retina in infantile spasms and that is directly observable. The observed damage resembles the damage in adults with severe damage to the peripheral retina and less severe damage to the central retina.

Data on visual damage in infantile spasms is mainly from ERG. The sensitivity and specificity of ERG for vigabatrin are largely unknown but may be low, and FDA is

unable to propose ERG or other testing recommendations for infantile spasms.

[Slide]

Individual case reports raise concern that visual disability from vigabatrin in some IS patients may be severe, although again the question is largely unaddressed.

[Slide]

The study design for examining vigabatrin retinal damage in all the available studies has been weak and ERG data, FDA feels, is questionable. And, the data that has been generated on severity, and frequency, and time course, and latency of damage, and the relationship to drug exposure, FDA believes that these issues have not been adequately addressed, at least adequately to know the answer to the question.

There are other questions that we talked about yesterday in adults. For example, does the visual damage progress once the drug is removed? And, that is an even more difficult question to answer because slow progression could be occurring over many years which would, after many years, have large consequence but, again, that small change each year would be very difficult to detect and that kind of

answer isn't available to us for patients with infantile spasms. Thank you.

DR. GOLDSTEIN: Thank you. Dr. Sheridan?

Clinical Studies in Infantile Spasms

DR. SHERIDAN: Good morning.

[Slide]

I am Dr. Philip Sheridan. I am a clinical reviewer with the FDA. In my talk this morning I am going to be addressing some issues we have with the clinical studies done in infantile spasms.

[Slide]

My talk will be divided into two parts, first to talk about the efficacy studies that were already presented this morning and, secondly, to talk about one of the safety issues, namely, intramyelinic edema which has been seen in animal models and the MRI abnormalities which have been observed in some human infants receiving vigabatrin. The other major safety issue, of course, Dr. Farkas has just addressed in his talk.

[Slide]

Now, the purpose of the clinical review of a new drug application is to evaluate whether the design, the

conduct, the data and analyses of clinical studies are adequate to determine that the drug is safe and effective in its proposed indication, and that the drug's benefits outweigh its risks.

For the purpose of brevity, I am going to be emphasizing not the substantial agreement that the agency has with the sponsor but particular issues in which we either disagree with the sponsor or have concerns that we want to be discussed by the panel.

I don't want you to have the impression that the agency does not take infantile spasms seriously. Of course, we do. We agree with the way this was presented this morning but we do want to allow maximal time for discussion from the advisory committee. As you will see, there are a number of issues that we would really like to get your input on.

[Slide]

Usually pivotal studies that support a new drug application are designed up front as pivotal studies. This was not the case in this particular NDA where the pivotal studies were done as academic studies. Therefore, some of the usual criteria that we have for adequacy of pivotal

studies weren't necessarily borne in mind as the studies were designed and conducted.

I would like to review some of these features because they will come up as we discuss the studies. We have a placebo or active control, with an adequate randomization procedure; an adequate blinding procedure, usually double-blind; a prospective choice of the primary endpoint; a validated method to assess the primary endpoint; a prospective statistical analysis plan, and we will put a good deal of emphasis on this because it solves a lot of problems and when it doesn't exist it can raise a number of problems.

Such a plan would include a prespecified analysis method; prespecified interim analyses if interim analyses are to take place; multiplicity adjustments to the p value in the event that multiple analyses are done, either as interim analyses or at the time of the conclusion of the study; and protection of blinding after an interim analysis is done.

It is important to adequately plan the study size with adequate power in mind; to ensure adequate patient enrollment with minimal dropouts; and an adequate treatment

period length to make the observations necessary.

[Slide]

Well, with those in mind, let's take a look at the studies.

[Slide]

As an overview, study 1A is a single-blind study. W019 is a double-blind study. FR03 is an open-label study. Again, they were investigator-initiated, not intended to support a new drug application and there are certain shortcomings that they have when used for this purpose.

[Slide]

Study 1A is a multicenter, randomized, single-blind study, single-blind in the sense that the investigators knew how the babies were randomized, which study arm, either low dose or high dose. The caregiver did not know to which study arm but the caregiver did know what the dose was. We have already reviewed this morning the high dose and low dose ranges.

[Slide]

The first phase is the single-blind phase that we are primarily interested in, lasting 14-21 days. This was followed by open-label follow up which went up to 3 years.

[Slide]

The primary efficacy endpoint is important to keep in mind. It was the proportion of subjects achieving spasm cessation for 7 consecutive days, beginning with the first 14 days of therapy, as determined by the caregiver assessment, and then confirmed by an 8-hour closed circuit TV EEG monitoring session done within 3 days of the 7^{th} day of spasm freedom.

Now, we would certainly agree with what the sponsor said several times this morning, that spasm cessation is really the clinical meaningful endpoint. I would also point out that the closed circuit TV EEG interpreter was blinded in this study, which is certainly a positive feature of this study.

[Slide]

The sponsor has presented its efficacy conclusion that with a p value of 0.0375 efficacy has been demonstrated. But there are a series of concerns that could impact on how much weight we can put on this p value.

[Slide]

Again, there was no prospective statistical analysis plan. The previous sponsor did not develop it. Of

course, the investigators had statistical methods in mind as they were doing the study and which they presented in their interim clinical reports. But an actual full statistical analysis plan was devised at the time that the current sponsor took possession of the trial data and was not fully agreed on until October of 2004. The study had been completed in 2002.

[Slide]

The sample size increased several times during the study and at that time there was no additional power analysis conducted to determine exactly what effect that would have. This reflects the original intent of the whole project, which was to make the drug available to patients and try to learn something about its efficacy in the process.

[Slide]

So, in looking at the data as it was presented to us when the NDA came in, we basically had three analyses. The first analysis was done, as you can see, in 1997. The sponsors indicated this morning that that analysis was done to have some data on the effect of vigabatrin in children at the time that the complex partial seizure NDA was being

submitted by the previous sponsor.

A second analysis which, again the sponsor said this morning, was intended by the investigators to be the final analysis was done in 1999 and in February, 2000 study report was submitted and subsequently published in 2001. The final analysis is the one that was presented by the current sponsor today.

In looking at this we noticed two things that caught our attention. The first was that we had a highly significant p value here and we wondered why the study was continued any further at this point. Then, with progression the p value becomes less impressive. Even more interesting was the fact that at this point for high dose responders there were 24 patients that responded, whereas when more patients were added the number of responders went down. That, on the face of it, didn't make any sense.

When we asked the sponsor about this, the sponsor explained to us that, in fact, when they took possession of the data, and they made allusion to that this morning-Bwhen they took possession of the data they used a more conservative way of defining who had responded and who had not in light of the primary response criterion of spasm

cessation.

We had some written correspondence back and forth on this during the summer. Our understanding of what happened is that when this analysis was done a responder was defined according to whether on the clinical research forms it had been indicated that spasms had stopped at the next clinic visit. Whereas, when the sponsor went back and actually looked at the exact timing as to what day the spasms stopped and what the seizure counts were they found that some of what was considered a responder at this time did not meet their more accurate designation of responder.

In order to understand the situation further we have incorporated these results onto sort of a timeline, which I think is consistent with the timeline that the sponsor presented to us earlier.

[Slide]

This is shown in this rather busy slide. Now, the columns that you have already seen are shown here, the first analysis, the second analysis and the final analysis. We have added some shaded columns which represent analyses that we did at the agency after the submission of the NDA to try to put these results into perspective.

In this first column we took the results from the first 44 infants, which was the original number that had been envisioned for the study. Using the statistical method that was used in the first analysis, we took a look to see what the p value would be. Whether such an analysis was done at the time by anyone is, of course, unknown.

At this point, by amendment 4 the size of the study was increased to 150 infants. At this point, again, apparently in support of the complex partial seizure NDA from the previous sponsor, another analysis was done, with a p value of 0.35. Then subsequently another analysis was done which was published in Neurology. This was done either in late 1999 or early 2000.

Now, given the fact that the current sponsor pointed out that they had an algorithm that gave them more accurate designation of who was truly a responder, we asked the sponsor to look at the data at this point in time and to reclassify the number of responders using their current algorithm.

We found the answer to the mystery of why the response went down. Using their current algorithm, the number of responders went from 24 to 10 in the high dose and

from 8 to 4 in the low dose. Using their designation, we then used the Fisher's Exact test to see what the p value might have been.

Now, we don't know whether anyone did a similar analysis at that time. We are dealing with a different sponsor quite a few years back at a time when it was not clear that the study was intended to be used to support an NDA. But moving along the timeline, we find that the study was increased at this point to 250 infants. Finally, we reach the current results.

Just for interest, within the agency we used again the Fisher's Exact test and got a p value that is a little less impressive but again in the same ballpark, which shows that the result may not be quite as robust as we would like to see but it certainly is within the same ballpark, which is reassuring.

[Slide]

We have already covered that.

[Slide]

To summarize then, this study originated as a compassionate-use IND. There were some changes along the way in the statistical analysis plan, with a formal

statistical analysis plan not being formulated until the study had been completed and all or most of the data analyzed, which is really backwards from the way that it ideally should be.

It is a single-blind study rather than a double-blind study that we would have like to have seen, and perhaps it is only partially single blind in that the caregivers knew the dosage and it might have been very natural for them to have compared notes with some of the other families that they might have encountered in the waiting room or in the community.

They may have been able to figure out, based on their dose, whether they were on the low dose arm or the high dose arm. It is also possible that some of the final patients were enrolled in the study after the Neurology publication was out.

Finally, there are a number of un-prespecified interim analyses with no p value adjustment. The p value adjustment would probably be minor but, again, this is an issue that could have been dealt with had there been a prospective statistical analysis plan.

[Slide]

The next study is W19. This is a double-blind, placebo-controlled, parallel group, monotherapy study. We, of course, like to see double-blind studies. There is randomization to either vigabatrin at 50 mg per day or placebo and, as needed, the dose was increased to a maximum of 150 mg/kg/day during the 5-day double-blind treatment period.

Now, we are a bit concerned in looking at this that the treatment period is only 5 days. That is very short. The rationale for that was that they wanted to minimize the placebo period for the patients.

[Slide]

The primary endpoint here is problematic in light of what has been said several times today, that the ideal endpoint would be cessation of spasms. Here we are looking at percent change in the average frequency of spasms assessed during a predefined 2-hour window.

[Slide]

Looking at the results, and I apologize for the handout, there is a typo in the handout with regard to the results. These are the same results that were presented this morning by the sponsor.

[Slide]

Looking at the primary endpoint at 2 hours, the p value is not significant. Now, it is true that if we look at the 24-hour endpoint and look for cessation of spasms we get a p value that is significant. However, this observation is not backed by EEG verification and, of course, is what we call post hoc analysis, done after the fact and, thus, we cannot put as much weight on the results.

[Slide]

So, in summary, the study was, in retrospect, rather small. The treatment period is quite short. The 2-hour closed circuit EEG window was too short, given spasm variability. Study 1A did better with the 8-hour window. And, the endpoint really should have been cessation of spasms.

[Slide]

The third study is a multicenter, open-label, 2-month crossover study of 23 infants with tuberous sclerosis and infantile spasms. There was crossover after 1 month. The patients were either on vigabatrin or hydrocortisone as an active control.

[Slide]

The primary endpoint here is the proportion of infants with total cessation of spasms. However, here there was no close circuit EEG confirmation or EEG confirmation so that we are dependent upon the determination made by the caregiver. As you could appreciate from the videotape shown earlier this morning, infantile spasms can be somewhat subtle and at times can be confused with normal infant movements, and vice versa. Again, here there was no formal statistical analysis plan.

[Slide]

The results certainly are impressive. They have already been reviewed by the sponsor.

[Slide]

The limits of the study are that it is limited to infants with tuberous sclerosis, which is both good and bad. There is no EEG confirmation and, most importantly, again this is an open-label study and for a study to be considered pivotal and to support an NDA application it would be necessary for there to be blinding.

[Slide]

So, in summary, it certainly is very impressive as supportive evidence for efficacy but cannot really be

considered a pivotal study.

[Slide]

We have some follow-on studies which are uncontrolled, open-label studies. Again, this is supportive evidence. It is very difficult, of course, to grapple with issues such as whether cessation of spasms has definitively been shown to alter the development course.

Finally, there is a question of whether treatment could be short term, weeks to months, rather than long term, months to years, which has not been addressed. Dr. Shields' comments on this are of interest and we would like to have the advisory committee's opinion on this.

[Slide]

With regard to the safety part of my talk and the assessment of the MRI abnormalities in light of preclinical intramyelinic edema, I am going to jump through a lot of my slides because I think they were very well presented by the sponsor already and we don't need to belabor the point.

[Slide]

We will stop at this slide. I think the question is still open as to whether the MRI lesions represent intramyelinic edema or whether they represent something

else. This will be addressed in the talk following mine.

[Slide]

This was covered by the sponsor.

[Slide]

With regard to conclusions, we would agree with the sponsor that there is a causal relationship between vigabatrin treatment of infants and the occurrence of MRI signal changes.

[Slide]

Is there evidence for clinical sequelae in the publications to date? No, there isn't but, again, absence of evidence doesn't necessarily indicate that it doesn't exist.

[Slide]

We agree with the anatomical distribution and with the fact that there is a suggestion but not a definite dose relationship.

[Slide]

The sponsor observes that the MRI abnormalities appear to be transient whether or not vigabatrin is continued. We think that this is still a bit uncertain given the fact that there is limited data from the two

retrospective studies and not all the patients had both baseline and follow-up MRI scans.

[Slide]

The sponsor concludes that these kinds of changes will not be seen in children greater than age 3. That appears to be true. We are not sure that it is an absolute cutoff beyond which there is no risk.

[Slide]

Again, it is not entirely clear that the MRI changes represent the IME that is seen in the animal model. It may, in fact, be the case that the MRI lesions may correlate with what was observed in the juvenile rat gray matter lesion that differs from intramyelinic edema, and this will be addressed by Dr. Schmued in the talk following mine.

[Slide]

In general then, within the agency we still feel that the MRI lesion is a problematic consideration that we don’t fully understand and will need to be weighed as you decide the benefit to risk for vigabatrin.

[Slide]

Overall then to summarize our issues with regard

to efficacy, the two pivotal studies, 1A and W019, are what we would regard as supportive studies. FR03 doesn't meet our usual criteria for demonstration of efficacy. The question of short-term versus long-term vigabatrin therapy for infantile spasms has not been studied and we would like your thoughts on this matter.

With regard to safety, there are still some questions about the significance of the MRI. Do they definitely represent IME? Are they always transient? Are they dose dependent? And, do they have clinical sequelae? Finally, we have continued concerns about retinal toxicity, as presented by Dr. Farkas. Thank you.

DR. GOLDSTEIN: Thank you. As we said earlier, Dr. Schmued, unfortunately, couldn't be here. He has his slides and he is going to be presenting to us over the phone. Dr. Schmued?

Nonclinical Central Nervous System Pathological Findings

DR. SCHMUED: Hello. I hope you can hear me. Thank you for letting me present. I am sorry I can't be there in person. Hopefully, I won't get the sequence wrong here.

[Slide.]

What I would like to do is review the pathology reports that were submitted by the sponsor for the vigabatrin and focus particular attention on the question of are the lesions of vacuolization seen in the juvenile rat comparable to what has been reported in the adult--in other words, intramyelin*ic that is reversible--or is it qualitatively something different.

So, with this in mind, if you would please go to the next slide entitled, "Findings of Study 1007." I will briefly review this initial study.

[Slide.]

This study, essentially, gave the animals vigabatrin for four to 60 days of age and, at the end of the two-month period, the brains were sacrificed and examined for vacuolization or other types of pathology. What the study found was that they did see vacuolization within the grey matter of the brains of the juvenile rats. These were found primarily in the forebrain. They did not show the characteristic intramyelinic edema, at least in its classical sense, associated with myelin.

Also, they did not report neuronal degeneration and they did use some stains specific for detecting neuronal

degeneration although there are some issues with the time frame that was used with this study. So I think, basically, they really didn't resolve what the cellular source of the vacuoles were.

[Slide.]

If we look at one sample data slide from this study, which is in the next slide entitled "H&E Photomicrographs," we can see here that, in the upper left is an example of a control substantia nigra. The lighter areas you see in the case are presumably blood vessels, the lumina blood vessels that you are seeing.

If you look at the area that, in the low back and left, is labeled "SC" for compacta, you will see that, in the substantia nigra compacta, on the right-hand, upper right photomicrograph at higher mag, this is a treated animal. You will see there are numerous vacuoles. They appear to be approximately the same size as the dopaminergic neurons that they seem to surround.

Another example of the pathology seen at higher mag can be seen at lower left and, in this case, these are the deep cerebellar nuclei. You can see that the vacuoles are virtually adjacent to the neurons themselves of the deep

cerebellar nuclei. They are fairly large, being at least as large or larger than the neurons themselves.

Over in the lower right, you can see that this low-magnification treated hippocampus, they show vacuolization. And one reason this was illustrated was because the hippocampus probably has the lowest amount of white matter of any nuclei within in brain. So it is a prototypical grey-matter area and would not have a lot of myelinated tracts in it.

[Slide.]

Okay. So, in terms of evaluating this study, if we go to the next slide entitled "Evaluation of Study 1007," we found credible the specific loci that the sponsors described as causing--as having vacuolization. And, also, the nature of the lesions seemed accurate within the limits of the experimental design used--in other words, within the limits of the survival time and the histological markers used.

The study, however, did not unequivocally confirm that there was not neuronal degeneration or, for that matter, that there was a degeneration of some other cell type such as astrocyte or oligodendrocyte, for example.

There was a follow-up study then, OVNC-9004, which, on the next slide, I have summarized the reported findings.

[Slide.]

In this study, they reported vacuolization in the mid-brain and brain stem. However, this doesn't mean that there wasn't vacuolization in other areas from what I could tell. I appears that, for some reason, the study was limited to just the mid-brain and brain stem.

And they reported that the vacuolization was of an intramyelinic-edemic nature and confined to the white matter.

[Slide.]

We can take a look at a sample of their data on the next slide entitled "Photomicrograph of Toluidine Blue Stain Sections." Again, instead of H&E, they used toluidine blue which is a fairly general histopathology stain which stains a lot of different structures.

If you look in the upper left-hand photomicrograph, you can see some tissue where the sponsors claim to have demonstrated demyelinization of vacuolization. This would be presumably in the deep cerebellar nuclei.

You can see there are some nerve cells adjacent to the arrows.

The arrows, themselves, the black one is supposed to represent the thinly myelinated fiber, the red one, an unmyelinated fiber, which, I don't know, is terribly convincing--or demyelinated fiber. I mean, there are unmyelinated fibers in the brain.

The actual, I believe it is a black arrow, is supposed to show some vacuolization but it is not clear that that is not just the lumen of the axonal sheath that we are looking at. And then the arrow that points to the large hole in the center doesn't look very compelling in terms of being a demyelinization or a vacuolization, I guess is what they are claiming, both in terms of size and in terms of the surround. There is no evidence of myelin surrounding this.

If, in comparison, we look over to right at the control tissue, you will notice that the actual lumen where the axoplasm, presumably is, is about the same size as in the treated. There are quite a few differences, however, in the orientation of the myelinated fibers. You can see there are many transverse-oriented myelinated fibers and there are virtually no neurons.

So this would seem to suggest that they are really not looking at the same area as in the treated case. This also, to some extent, can be seen in the lower illustrations. On the lower left, it is apparent that there is neuron staining. The arrowheads allegedly indicate vacuolization but, again, it is not really clear that there is much difference between this and what you see in the control on the right.

Again, the control in the right appears to have considerably more transverse grey condensed myelinated fibers or TRACs than the treated tissue shown on the left.

[Slide.]

So, if we go to the next slide, in terms of evaluating this study, the 9004 study, even though they are reporting intramyelinic edema which is typically associated with white matter, those areas that seem to show some effect would tend to be the grey-matter structures such as the deep cerebellar nuclei rather than the adjacent myelinated tracts such as a cerebellar peduncles.

Many examples shown in the tissues of the treated animals look qualitatively different than that of the vehicle controls. In other words, it really doesn't look

like they are looking at comparable regions.

Also, the study, another limitation was the fact that, except for, with the possible exception of one animal which had some data for the hippocampus, they didn't seem to look at any forebrain regions. It was all confined to the brain stem and mid-brain.

Lastly, as in the previous study, there were, I think, limitations relating to non-optimal survival times and concerns over the nonspecificity of the histological methods that were implied.

So let me address some of these general concerns that should be considered when designing this kind of study and interpreting it.

[Slide.]

If we go to the next slide which is entitled "Appropriateness of Survival Intervals Used," here I am just trying to make a real simplistic slide indicating the variability in species of this critical period of brain development in which there is increased natural apoptosis.

When the brain develops, what happens is more neurons are produced than it ultimately needs. Based on the connectivity and subsequent activation of these neurons,

those that become active survive. Those that are not active will die by natural apoptosis.

So, if you want to compare this, if you will, window of apoptosis of increased cell death in different species. You can see in the rat, it extends from approximately birth to two weeks of age. In the monkey, it can range from anywhere from maybe one month to three months of age and, in the human, it would extend up to three years of age.

[Slide.]

(9)If we can go to the next slide, I would like to show the importance of picking of the important survival time for looking for this type of pathology. Now, this example here, which the title indicates is kainic-acid-induced neuronal degeneration, is a completely different class of neurotoxicin. It is a cytotoxin. And this was used in the adult also, so it is dissimilar from that sense.

But, nevertheless, I think it still allows one to see the point that, if you look at a fairly short survival time after the insult--for example, two days--here, in the thalamus, you can see there is just massive neuronal degeneration.

We used a stain that we developed here at the FDA called Fluoro-Jade, Fluoro-Jade-C in this case, which stains the degenerating neurons as well as the neuropil and terminals which you would see at higher magnification. So, if we look at an animal that received a comparable dose and exhibited the same amount of seizure activity 30 days later, you can see that there is a vastly reduced amount of labeling of degenerating neurons.

So you can imagine that, if a study is looking at natural apoptosis, which occurs much more rapidly, anywhere from hours to a day or two at the longest before the neuron is totally absorbed, and you are looking at a longer time frame, namely 60 days, there is good chance that any neurons that degenerated early on in this vulnerable window would no longer be around and be able to be detected at a 60-day sacrifice time.

[Slide.]

If we can go to the next slide, let me just review the importance of using the appropriate histochemical technique to identify these types of pathology.

The first study used hematoxylin and eosin, that is the most common histological stain, and that will allow

one to see primarily the nuclei and cytoplasm in all cells. The second study used toluidine blue which will essentially stain your plasma membranes and the nuclei.

Although these stains have widespread use in conventional histology because they do stain so many different cell types, they have limited use in terms of trying to identify a particular cell that has been affected because of this lack of specificity.

Therefore, for example, if you wanted to detect degenerating neurons, one option would be to use these fluorescent Fluoro-Jade dyes, either the B or the C. They will detect degenerating neurons regardless of the mechanism of degeneration, whether it be necrotic or apoptotic.

This stuff is fairly recent but there are other methods dating all the way back to the '50s such as those developed by Wally Nata, the suppressed silver, in particular. These, although more labor intensive and capricious, can provide useful information and they will stain necrotic and apoptotic neurons.

Capsase-3 immunohistochemistry is another option. This will label only presumably apoptotic cells and not the necrotic cells. Perhaps I should have mentioned on this

chart that there are more specific, or certainly better, indicators of myelin damage as well, one being the Black-Gold dyes that we developed here which will give very high resolution staining or there are the immunological approaches such as the stain for myelin basic protein which will allow high-resolution staining of the myelination.

[Slide.]

Let me show you some examples on the next slide. It is entitled, "Photomicrographic Examples of Specific Stains for Myelin and Neuronal Degeneration Detection."

What we have here are tissues that were treated either with 3-nitropropionic acid. This is the top panel. This is an inhibitor of metabolic respiration or, in the bottom panel, kainic acid. This is an excitotoxin. The purpose of this is just to show the advantage of specialized stains for detecting these types of pathology.

You can see that, in the upper left-hand corner picture, we have a picture of the striatum following exposure to 3-nitropropionic acid. Even at this resolution and magnification, I think it should be very obvious that there are a number of varicosities which represent these edematous blebs that can be found along the myelin sheath.

You can see fragmentation and this beaded-chain type appearance which is very characteristic of intramyelinic edema. It can be detected both in the fine fibers between the fascicles of the striatum and the fascicles, themselves. Also, if there is no myelin--in other words, if there is demyelination--you will see a pallor as can be seen in the piriform cortex in the lower left-hand corner insert.

Going down to the bottom-left picture, again, this is the Black-Gold tracer following exposure to kainic acid. The magnification is a little low, but still there are a number--you can see that there are many fragmented fine myelinated fibers throughout the hippocampus. The arrows indicate some of these edematous-type swellings.

Moving over to the right-hand column, this material and their adjacent sections was stained with Fluoro-Jade-C which is a marker of neuronal degeneration. 3-nitropropionic acid will affect primarily the striatum adversely and result in a very large lesion in the center which you can see here. The degenerating neurons appear as the bright-green dots and the neuropil and axon would appear as fine fibers and terminals if we were to look at higher

magnification.

The dark spots you see are the actual fascicles, the myelinated fascicles, and then also blood vessels will appear dark, the lumina blood vessels. Lastly, in the lower right, tissue exposed to kainic acid, and this is stained with the Fluoro-Jade tracers, you can see that virtually all of the neurons in the CA1 region of Ammon's horn of the hippocampus has stained positive for Fluoro-Jade indicating they are degenerating as well as their basilar dendrites.

[Slide.]

If we could move on the next slide, I would like to briefly address the importance of picking the appropriate anatomical region to examine. I think the first study did a pretty good job of this in terms of examining a wide variety of anatomical regions including the forebrain in which they reported a number of regions which showed vacuolization. Their demonstrations seem credible in this area.

I think that it is important to look at the forebrain as they did because it contains a high grey-matter to white-matter ratio. So, if you are looking for neuropil or grey-matter pathology, it would be an obvious place to look. It employs the inhibitory neurotransmitter GABA.

Since vigabatrin has been indicated to act on the GABAergic neurons, and it has been suggested that it may actually be the axons of these neurons that are the site of the pathology, it would seem important that we look at this area that uses the appropriate transmitter.

Also, the forebrain develops last ontogenically. So, therefore, you would expect the critical window to be latest and, therefore, you could pick up a degeneration at the later survival times.

[Slide.]

The next slide, which is continued, essentially is just the converse of what I just said. The limitations of the follow-up study, 9004, which looked at really only the brain stem and mid-brain, were limited because they had had a lower ratio of grey matter to white matter so it would be less easy to pick up grey-matter pathology.

It employs inhibitory neurotransmitter of glycine instead of GABA so, presumably, these neurons are not the target of the drug. And it develops early so the cells would undergo apoptosis, disappear soonest and, therefore, would be the hardest to detect once they are gone.

[Slide.]

Let me now just go the next slide and briefly review other drugs which have been used for preventing seizures and convulsions that have been demonstrated to show a pathology, namely an increased neuronal degeneration when given during this critical period in experimental animals.

You can see midazolam is a GABAmimetic drug and it will cause pathology. Also, the NMDA-receptor antagonist, ketamine, will cause pathology. Valproic acid also has been shown in the juvenile animals to result in neuronal degeneration. This, it should be pointed out, is a GABA-transaminase inhibitor as is vigabatrin. So it may be some relevance there.

[Slide.]

If we can go to the next slide, let me just summarize some of the findings here. The first study and the associated review by the pathology working group seemed to constitute a relatively credible study by identifying correctly the grey matter lesions that were involved in this lesion and identifying them as distinct from the classic reversible intramyelinic white-matter pathology seen in adults.

Their inability was primarily that of not being

able to conclusively identify these cells or the source of the vacuoles. This may reflect simply suboptimal survival intervals which I will touch on briefly a bit more.

[Slide.]

If we can go to the next slide summarizing the follow-up study 9004, this was found to be somewhat less convincing in demonstrating the lesions were of an intramyelinic edemic nature. A number of problems were associated with the absence of degeneration in the grey matter may have been compromised to some extent by a bias in the anatomical regions that were examined--they just have that many grey regions--as well as less-than-optimal survival intervals and less-than-optimal histochemical techniques employed.

[Slide.]

If we can go to the next slide, let me just briefly review a possible experimental design that might be better in terms of resolving the exact nature of this vacuolization. This slide should be entitled, "Suggested Experimental Design for Unequivocal Resolution of VGB Lesions in Juvenile Rats."

First of all, I think it would be worth

considering dosing at two, or possible three, different starting times, 4, 7 and 17 days post-natally. The reason for choosing these times would be 0 to 4 days would represent a pre-term human infant in terms of development of the brain. A 7-day juvenile rat would be equivalent to a full term human infant. A 6- to 12-month old human would be modeled best by a 14-day-old rat. So it might be worth looking at those three times starting the dosing.

And then, equally, or more importantly even, is using an appropriate survival interval, not waiting two months to look for pathology which, by then, may be mostly long gone but using shorter survival intervals.

I would recommend considering 8 hours after dosing, 1 day, 3 days, 10 days and 30 days after the initial start of dosing. Depending on the nature of the degeneration and on the marker used, there may be some variability but I think this would certainly pick it up if one were to use this range.

Then it would be definitely worth using histological stains that are specific for the endpoints that one is looking for whether it be neuronal degeneration, myelin pathology, glial hypertrophy and so on. Again, for

detecting neuronal degeneration, there are a variety of methods that are all good. The Fluoro-Jade dyes, the suppressed-silver and the capsase-3 immunohistochemistry are all acceptable methods.

Myelopathies can be detected with recently developed Black-Gold bright-field tracer that we developed here or with more conventional myelin basic-protein immunohistochemistry.

[Slide.]

On the next slide, it just sort of follows up how one would analyze this. This is, I think, pretty straightforward. One would simply look for degenerating neurons, count the number of degenerating neurons and myelin lesions observed and compare this with an untreated animal of comparable age.

Again, I think it would be important to look at all the brain regions examined in the initial study including the grey regions, the grey-matter regions, of the forebrain.

[Slide.]

So that pretty much leads us to the conclusions which is on this final slide here. In developing animals,

it would appear that VGB exposure can result in lesions of the neuropil and grey matter of the brain. This lesion appears to be quantitatively different from the reversible intramyelinic edema reported for the adult.

It also should be mentioned that this type of edema that they are showing is qualitatively different then the intramyelinic edema reported for virtually any of your prototypical demyelinators, an agent like quiquinol, isoniazid, organotins or non-polar solvents.

In this case, typically your white matter show extensive vacuolization. So, for example, if you are looking at the cortex, the deep layer below Layer 6 where the corpus callosum is, will have extensive vacuolization. Then, as the myelin radiates out and becomes less dense, the amount of vacuolization becomes less dense. We really didn't see that pattern in the data presented here.

Also, it seems like the possibility of irreversible neuronal degeneration or, for that matter, the degeneration of other cell types, possibly oligodendron site prototypical cells, should be considered. This may be resolved by using shorter survival intervals and by using specialized histochemical stains.

[Slide.]

Just lastly, I would like to thank the people who have helped me with this presentation, my FDA Commissioner Fellow Sumit Sarker who helped put this Powerpoint presentation together; Ed Fisher and Lois Freed for inviting me to be involved in this; Tamy Kim for keeping me up-to-date and in the loop; my Division of Neurotoxicology out here at the National Center for Toxicological Research; and people, consultants, who are experts just in the use of sedatives in juveniles whether it be in the in the research arena such as John Olney at Washington University in St. Louis or Harley Kornblum who is a clinical pediatric neurologist at the University of California at Los Angeles.

Thank you very much.

DR. GOLDSTEIN: Thank you. Before we go back to being able to address general qualifying questions and pick up clarifying questions, pick up where we left off, I thought we should first just focus on the pathology since Dr. Schmued is on the telephone and he needs to go.

So, first, any questions? Dr. Dure?

DR. DURE: I have a question for Dr. Schmued regarding the kainic acid slide and I guess it is the

Fluoro-Jade. You showed, I think, an acute pathology slide and then one 30 days later. The one 30 days later, would that have shown pathology with more routine stains like H&E?

DR. SCHMUED: I suspect not. Obviously, I don't have the data in front of me to tell you, but what you are seeing mostly at the 30-day time is the transneuronal degeneration. The neurons that were the primary target of the kainic acid have degenerated and, at this time, you are seeing some degeneration.

It is possible with H&E to infer some types of pathology. For example, there is an increased eosinophilia and often you will see a pycnosis and shrinking of neurons. However, this is not always that consistent. It will be only seen at certain times and often, if you have used the stain, you will know that you will get stains that are just a shade of lavender. It is not really clear whether they are degenerating, whether they are sick, whether they are going to get better or what.

So, you know, the kainic acid was a very extreme case. I mean, this is a sledgehammer, literally. And it is in the adult. These neurons will take up to, typically, two weeks to degenerate completely. This is in contrast to

apoptosis-induced neuronal degeneration like as has been reported for ketamine.

Often this, within anywhere from hours to a day, will be completely absorbed because these cells are so much smaller and haven't really differentiated. So, I think the odds of seeing anything at 60 days are almost nil.

DR. GOLDSTEIN: Dr. Jensen.

DR. JENSEN: Yes. I really agree strongly with Dr. Schmued's presentation and I think there were probably more up-to-date techniques that could have been used on these experiments. But, just to put this in perspective--because this comes up quite frequently with respect to this increase in constitutive apoptosis that has been noted for a variety of currently clinical used agents including GABA agonists such as phenobarbital and some of the benzodiazapines, as you have mentioned.

While there is evidence in animals, rodents, for this and some non-human primates, there is no evidence I am aware of, and I would like to ask Dr. Schmued if he is aware of this, actually in humans that have been from post mortem material that have been treated with any of these agents.

I think there is a great deal of controversy in

the field as to the relevance of this increasing constitutive apoptosis in otherwise normal animals as opposed to the animals that would have some process like epilepsy and then were subsequently treated with these drugs at these doses, and also humans that would have been--you know, epileptic humans that are treated with these drugs.

So I think the issue of constitutive apoptosis, I think we have to be very careful in how we think about it because I don't think its relevance to humans has yet been conclusively determined.

DR. SCHMUED: Yes. I, for the most part, would agree with what you say. As you say, this has been demonstrated in the primate. And, in the primate, as work we have done down here with ketamine, Chen Lang being the P.I., we do see that, within the first three months of ketamine exposure, an increased apoptosis. But, again, I am just going up the phylogenetic scale. This is a monkey and not a human.

But, of course, as we all know, humans can't be treated like experimental animals so it is hard to get autopsy material that is within this important clinical time frame. I haven't done a comprehensive study of the field of

what has been reported in the human infant so I don't know that.

But I would agree with you that an infant human having seizures is not identical to a normal rodent and, at some point, it becomes a benefit-risk assessment. That is kind of out of my area of expertise. I am just talking about the pathology. But I would defer to my colleagues at the FDA to evaluate this, the risk-benefit, aspect which it almost sounds like this is touching on.

DR. GOLDSTEIN: Dr. Schmued, Dr. Goldstein. Can these stains, these special degenerate stains, can they be done on tissue that has previously been stained or previously preserved and stored, or do they need to be done on fresh tissue?

DR. SCHMUED: They are pretty robust. Now, the Fluoro-Jade stains in particular can be used on tissue that is archival. There might be some slight degradation in some of your more subtle labeling like the fine terminals but yes, certainly, the conspicuous labeling of axons and the cell bodies would be no problem.

And you can use the Fluoro-Jade dyes either in embedded tissue or frozen-cut tissue so that wouldn't be a

problem. The Black-Gold stain for the myelin is only suitable for frozen tissue and not paraffin-embedded tissue. So I can't really remember how this was cut.

But if it was frozen sections and they were kept moist, we have gotten good staining out to a year after sacrifice. So I think there is a reasonably good chance that they could be restained.

DR. GOLDSTEIN: So, could some of the tissue--I don't know whether the people who did the studies actually have it. There may be some possibility of doing some of these stains in other brain areas that hadn't been stained previously or even in the areas that had been looked at.

DR. SCHMUED: Yes. Like I say, the Fluoro-Jade dyes will work with either embedded or non-embedded tissue so I think there would be a very good chance of that working and, if they did use frozen sections and had wet tissue left, they the Black-Gold would also be good for the myelin staining as well as the myelin-based protein immunohistochemistry.

DR. GOLDSTEIN: Thank you. Dr. Twyman?

DR. TWYMAN: Thank you. I just want to raise a point of consideration on the valproic acid observation in

the apoptotic neuronal degeneration. Valproic acid is a well-known HDAC inhibititor, a cystone deacetylase inhibitor. This mechanism has been well-characterized in apoptosis also. So I just wanted to raise that as a point of consideration.

DR. GOLDSTEIN: Thank you. Any other clarifying questions from the committee about the pathology?

Seeing none, let's go back then to the general clarifying questions. As, as we did yesterday, this tends to blend between both the FDA presentations and the sponsor presentations. And this is on the FDA but it is really both together.

So, let me start off, again, with Dr. Temple with whom we left off before.

DR. TEMPLE: My questions are about study 1A, and they could either go to Phil or to Dr. Shields. The sponsor, on Dr. Shields' slide 8, showed a fairly striking difference between patients who were considered spasm free based on the 3-day window, which was specified, and people in whom the EEG was allowed to be outside that window, judging from their written materials on page 120 of the book, as much as 10 days afterward. But, if I understand

it, they had to continue to be spasm free, at least to the observer, in order to get the electroencephalogram. Right?

So, you make the point in there, although this hasn't come up here, that in some sense that is a more conservative measure because they have to be spasm free for longer than the 7 days so we shouldn't worry about it.

You still can't tell from anything that is written what fraction of people who were nominally spasm free according to the observer actually ever had an electroencephalogram. So, did most of them? And, how was that decided? Some of them just gave up, or what happened?

DR. SAGAR: We have a flow chart--

DR. GOLDSTEIN: Sorry, just say your name for the record, please, so the reporter knows.

DR. SAGAR: Oh, I am sorry. I am Steve Sagar, from Ovation. We have a flow chart I believe that shows that.

DR. TEMPLE: I should say I ask this because the concern about the marginal statistical value and the number of the points Dr. Sheridan raised would be less striking if the p was something like 0.001. You would worry less about multiple looks and a variety of things if that were true.

DR. SAGAR: So, by caregiver report there were 74

subjects who were spasm free for 7 days, beginning within the 14 days. Of those, 34 had video EEGs and spasm freedom was confirmed in 25 of those. The other 42 either did not have a video EEG or it was not done within the 3-day time frame. And, you can see what happens to the ones that weren't done in the 3-day time frame but were done. So there were only 4 subjects of the 74 that did not have a video EEG after being reported to be spasm free. Does that answer your question?

DR. TEMPLE: Sort of. So, the values you gave on slide 8 show that for the people who were allowed to have their EEG at some time outside the window, but were still spasm free, the nominal significance is something like 0.001. A table you have in the text shows a wide variety of p values calculated for allowing 3 days, 4 days, 5 days, 6 days, minus 1 day, 8 daysB-a lot of windows, and they are all considerably better than the 3-day window one.

I don't know whether Phil has any comments about that either. It doesn't seem a crazy thing to do because you are still getting the electroencephalogram. I guess the other thing that strikes me is that the observers thought almost everybody was spasm free for at least 7 days. The

results were over 75 percent.

DR. SAGAR: I am sorry?

DR. TEMPLE: If you look on page 121 of your thing, patients with spasm cessation for 7 consecutive days, although some of these could have relapsed, were 78 percent in the high dose and 76 percent in the low dose. That is the observer saying no spasms. Well, that is an incredibly high rate compared to the rate you eventually confirmed on electroencephalogram.

DR. SAGAR: That was during the entire study, including the follow-up period. What I showed on the flow chart was the ones that were spasm free within the first 14 days of treatment. So, this is long term, the table you are looking at is long-term follow-up data, not the short-term response observations.

DR. TEMPLE: Okay. In some ways that is even more impressive. That says going out for the whole thing something like 68 percent on the high dose were spasm free and 52 percent on the low dose were spasm free for the whole time, which is considerably larger than the numbers that were confirmed electroencephalographically, but that could be because a lot of the people who were spasm free never had

an EEG. So, it might have been higher if they had been done. Is that what you are saying?

DR. SHIELDS: Don Shields, UCLA. Let me make a couple of comments. The first 3 days, the fact that you have to have the EEG in that period of time clearly underestimates the efficacy because it was just difficult to do. I think that later allowance of time is a much more realistic result of the numbers.

These later numbers have two confounding variables in them. One is they did not require an EEG so this is parental observation. You saw from the slide that was previously given why we require the EEG confirmation, because the spasms may go from what you saw, very dramatic, to little tiny head drops that the parents may not perceive. So, that is why we need the EEG. So, I think the 78, 76 percent is probably an overestimate of what really happened.

The second confounding variable is that after 30 days we might have added in ACTH; we may have added in topiromate. There are other drugs that are allowed to come in. This is best clinical practice at that point. So, I think this is what you can do when you are doing everything you can do to try to get them controlled, but I think those

higher numbers-Bit is not necessarily fair to attribute it exclusively to vigabatrin.

DR. TEMPLE: Okay, but for the study that you are willing to attribute you think the values shown on your slide 8 are a better representation of what actually happened because it allows you to go outside that window and it was hard to get people tested within the window.

DR. SHIELDS: I think that it is a much clearer representation of the reality of the results, yes.

DR. TEMPLE: Okay. I am still interested whether Phil has any thoughts about that because, you know, it makes a lot of other worries smaller beer because your p value now is at 0.001.

DR. SHERIDAN: Again, ideally certainly a more liberal time period for obtaining the EEG confirmation would have been stated up front. When we look at a number of possible outcomes from the study and pick the one that makes the drug look the best, then you have concerns that you are no longer... [inaudible].

DR. TEMPLE: That is fair enough. It is worth saying, as the company said, that it is more conservative. You have to be more sustained in order to do that. So, you

might have thought it would work against the observation. Thanks.

DR. GOLDSTEIN: Dr. Dure?

DR. DURE: Thank you. I have two clarifying questions, one for Dr. Sagar. When you talked about one of the uncontrolled IS studies, 332.5, did you actually say that that included children up to the age of 12?

DR. SAGAR: Yes, those were children with infantile spasms who had been unresponsive to prior treatment. It is rare but there are cases of infantile spasms persisting later in childhood.

DR. DURE: Okay. My second question, Dr. Pellock mentioned a few times manageable risk, and this question is not necessarily directed to Dr. Pellock but I have a question for the sponsor. Is there any data that confrontation is in any way reliable for detecting mild to moderate peripheral visual field defects in children under the age of 6 months?

DR. SAGAR: I would have to defer to Dr. Sergott about whether there is data to address that issue.

DR. CUNNIFF: I would just like to add too that one of the ways that we manage risk is through the REMS where we

have the mandatory efficacy assessment at that 12-week period. So, those patients who are not responding to vigabatrin, they will be removed from treatment. So, that takes away some of the risk as the risk increases over time for developing a PB so that is one way to get it, and Dr. Sergott will address the confrontation testing which is another way.

DR. SERGOTT: Bob Sergott, Wills Eye Hospital, neuro-ophthalmology. I am not aware of any data about confrontation testing in that age group. We all use it clinically and after a while, as Dr. Pellock said, you get fairly comfortable with this and can pick up gross deficits. I would say moderate you can probably detect; mild probably not. I don't know if any other of the ophthalmology people on the committee have any experience with this.

DR. GOLDSTEIN: Dr. Repka?

DR. REPKA: Michael Repka, Baltimore. You know, I was going to get to some clarifying questions on fields and ERG in a moment; I can't think of any other reason I am here. But these are both extraordinarily problematic to do in this age group. In absolutely normal circumstances I would actually answer my colleague on the panel that I think

in a 6-month old with spasms I wouldn't believe the results that I got with confrontation fields. I think the sensitivity of my testing would be hopeless, really low.

There are no data, of course, in even a normal population of our ability to pick up defects in a child who has had a brain tumor, and actually test us against a known anatomic deficit. So, I think there are no data.

I think the other thing to remember as we evaluate risk hereB-I have learned a lot about infantile spasms from Dr. Shields. The problem here is that they are going to be treating these kids for a short time. They are going to know a result.

I think the large bulk of our data that we know about vigabatrin and retinal toxicity is that there are estimates of about 30 percent, and I think the point is well taken by the agency that it could happen, maybe start to happen quickly. But then I think, as Dr. Shields alluded to, by a year the dose is coming down. Am I quoting you correctly, Don?

So, I think that is the perspective here. So, this testing-Band we are all struggling with this because we want to look for a signal where there is a real bad problem

in just one patient as something that maybe the window of treatment allows us to be in a safety zone.

DR. GOLDSTEIN: The last person on my list before the break is Dr. Weinstein. Do you have a question still in mind from before?

DR. WEINSTEIN: A lot of these kids are visually inattentive. I mean, oftentimes that is what brings them into the office. It is not that the parent thinks the child is seizing but the child no longer pays attention to the environment around them, and it is a stretch to think that I am going to be able, and have been able to test them. So, I agree with everything that has just been said.

DR. GOLDSTEIN: And a good follow up is Dr. Repka. You had some issues or things to clarify about the visual testing?

DR. REPKA: Michael Repka. I was interested in hearing the sponsor on what they think the availability of electroretinography would be in the population if this drug were released to widespread or wide-scale utilization. They have certainly acknowledged that it is a specialized test. It is not widely available.

And, I suppose you talked about that with adults

yesterday. But I would actually like to point the question to the pediatric population, and could we see labeling of a product that in fact it is impossible for the practitioner to comply with because there is no availability of the clinical test?

DR. SAGAR: I think the sponsor does acknowledge that this is not readily available in the United States for this infant population. I will let Dr. Cunniff comment on our labeling.

DR. CUNNIFF: I think in putting together our REMS, which is largely similar between both patient populations, for the adult complex partial seizures patients we are mandating that visual testing is done. We aren't mandating it for the infants for the very same reasons that are just being discussed right now.

We do think it is a very different benefit/risk proposition between patients with complex partial seizures and patients with infantile spasms so we are comfortable with that position. We do know, as Dr. Pellock pointed out earlier, that these patients are seen very frequently and a neurologist is looking and trying to do what he can to do some confrontation fields on those patients, and looking for

motor abnormalities which could be suggestive of something with the MRI.

Dr. Sergott, I don't know if you want to add to the discussion of how the neuro-ophthalmologist might inform some of these discussions. But that is why we have set the REMS up the way it is because we agree that if we enforced the visual field tests we wouldn't have any patients on the drug to a large extent.

DR. VAN BELLE: Yesterday Dr. Faut suggested that infantile spasms were part of complex partial seizures. Dr. Shields suggests otherwise. I think it is important in terms of if the mechanism of action in infantile spasms is part of the complex partial seizures, then that makes the issue of efficacy a lot easier than if this is a very distinct entity. So, could I get some comment on where infantile spasms are relative to complex partial seizures?

DR. SHIELDS: Don Shields, UCLA. Complex partial seizures may precede, accompany or follow infantile spasms. That is not the most common situation. The etiology of infantile spasms is virtually anything that can damage the brain.

I actually had a slide which we can't seem to

findB-if you have it we can put it up--that has all of the list of things. You know, hypoxic ischemic encephalopathy, tuberous sclerosis, brain development abnormalities such as hemimegaencephaly or focal dysplasias, metabolic diseases. It is a huge differential diagnosis and many patients will present only with infantile spasms and no partial component to it. Patients who have a focal cortical lesion may have partial seizures accompanying or following spasms. So, it is not an either/or.

[[Slide]

That is it. So, that is a list of things that is associated with infantile spasms. The yellow box are things you learn by history. The green box are things that you learn by physical examination. The red box are things that we pick up from the MRI scan. The white box below are all the things we have to do with metabolic diseases when we haven't found it with the others. What is left over goes into that idiopathic, cryptogenic category. That is maybe a third.

DR. GOLDSTEIN: Dr. West?

DR. WEST: This is Connie West, pediatric ophthalmology, Cincinnati. I would like to revisit Dr.

Repka's question about what it is exactly that we, as ophthalmologists, are being asked to do at these ophthalmic surveillance visits. Because in my almost 20 years of experience seeing children with seizure disorders at a tertiary care hospital, many of the children are somnolent while they are at the visit. They can't even have their visual acuity tested, let alone confrontation visual fields. It varies from time to time. Sometimes these families are traveling from a great distance.

I don't really know that what I find on my examination is going to influence whether or not the medication should be continued. Because how do I know from day to day if my assessment of their visual function is due to their intrinsic brain pathology? Is it due to a medication side effect? There is clearly no way to sort it out. So, I would feel badly making these families come in if it is not necessarily going to change what the pediatric neurologist chooses to do.

My other comment was on the sponsor's assertion that these should be prescribed by board-certified neurologists, but I would also point out that pediatric neurology has a separate certifying board and it would need

to include board-certified neurologists as well.

DR. GOLDSTEIN: Thank you. Dr. Chambers?

DR. CHAMBERS: In response to an earlier question, it was my feeling that there is some data on follow up of visual fields from the Boston group. Is that data that has been submitted to the agency? Did I just miss it?

DR. SAGAR: No, sir, that has not been submitted to the agency. That is just in the form of a publication, a preprint of a publication.

DR. CHAMBERS: And I assume that it will be submitted to the agency sometime in the near future?

DR. SAGAR: Yes, sir.

DR. CUNNIFF: It is unpublished data right now so as soon as it gets published we will get it in.

DR. CHAMBERS: I mean, the agency did request all information of that form.

DR. GOLDSTEIN: Dr. Katz?

DR. KATZ: I have several questions about some of the efficacy data. We heard a number of people whose language was, like, the drug works within 2-4 weeks, so works within 4 weeks. But just as an example, I guess Dr. Sagar's slide 12 which describes the study design for FR03

which had a 4-week period and then there was another 4-week, the conclusion from this was that everybody, on the first slide on vigabatrin, responded within 4 weeks, and then I guess the 7 who were switched over responded within 4 weeks. But what does that mean, responded within 4 weeks? Does that mean for the entire 4-week period? How long were they spasm free in those various periods?

DR. SAGAR: I will have to check to be sure, but I believe they were required to be spasm free for 48 hours.

DR. KATZ: It might be useful to see the distributions of durations of spasm free. It is one thing to say spasm free for 48 hours; it is another thing to say spasm free for 4 weeks or for 2 weeks as opposed to within 4 weeks. So, that might be useful information to see.

DR. SAGAR: I will see if we can get it for you.

DR. KATZ: Distributions of the spasm free. The other question I have had to do with the U.K. study, which I guess is slide 25, or this particular question relates to slide 25. This is where patients were randomized. I don’t recall if this was open-label or not, but they were randomized to so-called hormonal treatment.

[Slide]

That is it, right. So, the 75 percent in both groups continued spasm free at 14 months. We have heard that at about the age of 1 year the spasms might sort of spontaneously remit anyway and there are other seizure types. So, I am wondering how to interpret that data. Does that mean that they still had all their other seizure types? They still had all their other problems? They just didn't have spasms? What exactly does that mean?

DR. SAGAR: I think you summed it up. These numbers have the same implications as Dr. Shields discussed with study 1A, that after the first 14 days of treatment these infants are treated with the best available medical care. They are treated in the ensuing time with a variety of agents in addition to those to which they were initially randomized. So, this means that at 14 months of age they had been spasm free for the priorB-it varied from patient to patient but about 3 months.

DR. KATZ: Okay, but I guess I am asking in addition a slightly different question, which is what would we have expected if they hadn't received any treatment at all with regard to their being spasm free at 14 months of age if spasms are largely done by then anyway? I guess I am

trying to get at that as well.

DR. PELLOCK: Jack Pellock. Dr. Katz, probably 20-25 percent go into remission completely, and the others go on to have some sort of epilepsy.

While I have the podium on record, child neurologists are board-certified by the American Board of Psychiatry and Neurology and, depending how old you are, it is either special competence in child neurology or special qualification in child neurology. So, there is something special about people who treat little kids with neurology problems.

There was another questionB-oh, about the vision. I don't think anybody is arguing that confrontation, you know, answers everything. Anybody who sees a kid would know that. But, on the other hand, with the repetitive questioning about the visual history and that close follow up, if there is a clue, then we are going to ask all of you, the ophthalmologists, to help us out in the best way you can.

DR. GOLDSTEIN: Dr. Kieburtz?

DR. KIEBURTZ: Thanks. I have sort of two questions. One is about the age distribution, and the first

of those goes to Dr. Sheridan. I understand from 1A, FR03 and W019 that there is only a handful, from your perspective, of subjects who were over the age of 24 months. Is that correct? It is actually listed in an appendix I don't have but I think it is about 5 or 6 people. Is that right? I mean, the average age is well under 24 months.

DR. SHERIDAN: I am not sure, are you referring to something that was in my review?

DR. KIEBURTZ: Yes, yours and the statistical review. Just how many subjects were in that combined data set. Their age at entry to those studies was about 24 months. Do you know that?

DR. SHERIDAN: I don't recall that offhand. I would have to look back and find that for you.

DR. KIEBURTZ: Okay. And, if I could ask the sponsor the same question about 332.5, 3E01 and UKISS. Do you know what proportion of subjects in those trials were above 24 months? And then I have one last question after that.

DR. SAGAR: I will have to, again, check and be sure. I believe UKISS had an upper age limit of 24 months or less. I don't remember the exact upper age limit but it

had an age limit. I will have to check the upper age limits on the other studies.

DR. KIEBURTZ: Because I just think for questions 6 and 7 that we will discuss this afternoon those will be relevant bits of information.

DR. SAGAR: Okay.

DR. KIEBURTZ: And, Dr. Sheridan, back to you, in those studies in which one could measure time until response, whether it be total cessation or some other response--now, I know 2 of those studies are short but, to the extent you could measure a time to response variable, do you have a sense of the mean and the maximum, or some measures of central tendency? Because what we are hearing, just to put in reference why I am asking the question, is that we will check at 3 months and if there is not a response we will revisit whether the drug should be used.

But if 90 or 100 percent are responding within 4 or 6 weeks why wait until 3 months? So, I am trying to get a sense of, if we could measure time to response, what that is. I guess I will just leave it as a question for now. Do you have a sense for that, Dr. Sheridan?

DR. SHERIDAN: Well, my sense is that if the child

was going to respond to vigabatrin that response was seen within 4-6 weeks. But I can look that over again and get back to you after lunch.

DR. KIEBURTZ: Because I think in figure 4 in your report about 1A the Kaplan-Meier shows some, you know, asymptotic behavior towards whatever that is. But if you could let us know your sense about that I would appreciate it.

DR. SHERIDAN: Certainly.

DR. GOLDSTEIN: Dr. Chugani?

DR. CHUGANI: It has been addressed. Thank you.

DR. GOLDSTEIN: Dr. Lu?

DR. LU: My first question is about data quality of study 1A. We know that 1A was not designed originally as a pivotal study so I wonder about, you know, the practice of data management and data quality control and FDA auditing afterwards, and in particular a couple of points came to my attention.

One was the discrepancy in terms of responders definition between the final sponsor's analysis and the original study analysis. Also, in the form in the background materials the FDA provided in Table 12, I noticed

for the first 44 patients before the first interim analysis the data was done in September of 1996. There were no responders in the placebo arm and there were 3 responders in the treatment arm.

So, 9 months later in the first interim analysis there were 11 patients added to the low dose group. There were 7 patients added to the high dose group and in each of 2 groups there were 5 responders. That 5 was actually a lot if you look for the second responders. So, it is a large proportion which is unusual within such a short time. I assume those will be the new patients because the endpoint supposedly was in 21 days.

DR. CUNNIFF: Tim Cunniff, from Ovation. I will make a few preliminary remarks then I will ask Dr. Sagar to add anything I have missed here.

I think, first of all, we agree with Dr. Sheridan's presentation about how one would normally set up a pivotal clinical trial. I think those points are well taken. I think, fortunately, for this study we had a very objective endpoint and when Ovation came in, in 2004, we did not accept the previous analyses done and the previous interpretations. We hired an independent CRO to go out

there and we verified all of the data against the actual source documents, 100 percent reconciliation. We also put together a statistical analysis plan.

So, it was done after the fact but we did it very rigorously, like any industry-sponsored clinical trial would have done. So, when we did everything and we put everything in place we were very surprised too that a very highly statistically significant response is what came down. But that is because we did our own analysis according to our specified plan and we 100 percent verified all of that data at the sites by using an independent CRO.

I would also like to put the p value in perspective. In our analysis it is statistically significant; in Dr. Sheridan's it may be a little bit above but in the same ballpark. I just want to remind the committee that this is a comparison to active therapy. It is not a placebo-controlled study. We are comparing a high dose to a low dose.

So, I think that if one, you know, can imagine if you impute a placebo control, no matter what analysis is done, the FDA or Ovation analysis, it would be statistically significant over a placebo if one had been present in the

study. Dr. Sagar or Dr. Bittman, anything you want to add?

DR. LU: So, are there any reconcilable data points? Because the data have been collected in the past. Right? Whatever you do retrospectively, you can't change those. So, basically are you satisfied with the data?

DR. CUNNIFF: We actually went to all of the 9 sites that participated in that trial, and we did not go to the clinical study documents that had been prepared by the prior sponsor, we went to the actual source data. So, I think we are very confident in our analysis.

DR. LU: Can I follow up? There are a couple of things I want to clarify. Dr. Temple just mentioned about the longer time in terms of endpoints, the smaller p values. But I was wondering, for the low dose group after 7 days, will they be able to switch to the high dose?

DR. SAGAR: Yes, after the initial 7-day treatment period the low dose group were treated according to their physicians' discretion and, in fact, the average dose of the low dose group very rapidly approached the high dose group over the ensuing couple of weeks.

DR. LU: So, in interpreting the data we should be very careful to stay within the given 7-day period--

DR. SAGAR: Absolutely.

DR. LU: B-as the drug kicks in very quickly. The other point is that I noticed in your slides earlier that in spasm cessation that was self-reported and confirmed by EEG there were 12 percent in the first group that actually were not confirmed, and also the second time there was 44 percent not confirmed. Right? If you bring up the early slides. In other words, perhaps we cannot rely completely on the self-report.

DR. SAGAR: I think that is a fair statement, absolutely.

DR. GOLDSTEIN: Dr. Nelson?

DR. NELSON: Thanks. Actually, that kind of asks a little bit what I was going try to confirm. Just so I can understand, maybe Dr. Sagar or somebody else might answer this, the clinical findings of spasm elimination have to be confirmed with EEG monitoring. Is that right? Is there a benefit clinically in long-term outcome to suppressing, you know, the clinical manifestations without fixing the EEG? I guess that is kind of a question.

In the W019 study-BI mean, the implication from the 1A study, what they were just discussing and Dr.

Temple's comments before, is that you need to improve the EEG to normal. Right? Whereas, in the W019 study it just said that the EEG was improved as opposed to normalized in these patients. And, it was only normalized in a fairly small number of patients relative to those that had spasm reductions. I mean, many patients had spasm reductions. It is not even clear if they were in the same patient group. So, could you just explain a little bit about the relationship of those two things?

DR. SHIELDS: Don Shields. I think the concept is elimination of hypsarrhythmia, which is different than making a normal EEG. You may have a child with tuberous sclerosis who has a tuber that has a very active flex spike focus going on and there may still be spike waves from that focus. So, that would not be a normal EEG but if the hypsarrhythmia is gone we would consider that a successful outcome. Does that answer the question?

DR. NELSON: Well, in W019 is that what the words improvement in EEG mean? I mean, it suggests that it just got back to whatever this person's baseline should be and we are satisfied with that.

DR. SAGAR: In the clinical study report of W019 it

is not specified more precisely than that, just that the EEG is improved.

DR. GOLDSTEIN: Dr. Temple?

DR. TEMPLE: Yes, I still want to make sure we understand A1. They were supposed to become seizure free within the first 14 days. Right?

DR. SAGAR: Correct.

DR. TEMPLE: So, up to that point they don't increase the dose. Right?

DR. SAGAR: Correct.

DR. TEMPLE: Okay, so if they did become seizure free, then they were supposed to have an electro-encephalogram within 3 days of whenever they completed their 7^{th} day. So, at what point in there would the dose go up?

I also note that if the dose goes up that should reduce the difference in the 2 groups and it seemed to get bigger so I don't know how much to worry about that. But structurally for the trial, if they had not achieved seizure freedom by 14 days, then they could enter the open-label phase at that point. If they had achieved seizure freedom, then they would be scheduled for a video EEG.

That has nothing to do with the analysis we are

talking about. That analysis is only done in people who are seizure free according to the observer and then get an electroencephalogram. So, the values in slide 8, that can only be people who were seizure free. Right? In that slide you show what happens if you insist on 3 days and what happens if you get an EEG at any time. But that is only in the population who was seizure free.

DR. SAGAR: That is correct.

DR. TEMPLE: So increasing dose is irrelevant to that, I would have said.

DR. SAGAR: In this analysis increasing dose is irrelevant. At the time of their EEG they were still on the dose to which they were randomized.

DR. TEMPLE: I just wanted to be sure of that.

DR. GOLDSTEIN: Dr. Crawford?

DR. CRAWFORD: Thank you. My questions will be directed to the agency, though I would ask that the Chair also allow the sponsor to comment if it seems appropriate.

I have general questions but wanted you to please help me understand the criteria for determining the adequacy of pivotal studies in clinical trials. My thoughts could be expanded to the presentation by Dr. Schmued on adequacy of

preclinical studies.

Information presented by the sponsor certainly is suggestive of their conclusions about the safety and efficacy of vigabatrin in the treatment of types of infantile spasms. We know that questions and comments, some of which are quite persuasive to me from the agency, from Dr. Sheridan's presentation regarding study designs, the methods, statistical analysis plans and interpretation.

A few moments ago Dr. Cunniff stated that those points are well taken, however, his response was that in their opinion the sponsor's re-analysis of those studies addressed it adequately.

Earlier some of the sponsor's responses to these same issues were that concerns could be allayed by frequent monitoring of the clinicians, the physicians if the drug product were approved for this indication.

So, my question, I would like clarification from the agency if possible, is about the minimum criteria necessary for determining the adequacy especially of the clinical studies. As an example, yesterday the committee considered the question from Dr. Temple about the need for a comparative effectiveness study.

Of course, that was for a different patient population where other products might be utilized. While very desirable information, there was not support from this advisory committee, perhaps because that was considered to be beyond the stated criteria for establishing safety and efficacy.

So, in conclusion, my question to the agency is what are the minimal criteria for determining that clinical studies are adequate and well designed, or is this always a subjective determination for each application?

DR. GOLDSTEIN: Dr. Katz?

DR. KATZ: Well, that is a big question. The answer, as the answer is to almost all questions, is that it depends. Phil showed you sort of the list of criteria for sort of an ideal study but even then it depends on the situation. For some studies you might not worry about blinding or lack of blinding. In some studies, even under certain circumstances, you don't need a concurrent control. So, it is going to be on a case by case basis.

The other thing, of course, is that no study is perfectly done. There are always people who drop out and that imposes certain difficulties in analyzing a trial. So,

I don't think you can say here are the things you need to have in an adequate study. You are going to have to really judge it on the basis of exactly what happened.

These are things we always like to see but, again, there are cases where they are not necessary, or the result is so overwhelming, or the outcome measure that you are looking at is so objective that maybe if the blinding isn't perfect you are not so worried. You really have to sort of look at the thing on a case by case basis. That sort of speaks to the question of what is an adequate study. I realize I didn't give you an answer.

Then there is the question of how much data do you need before you can approve a drug in terms of one study versus two studies. That is another question. Typically, we require independent replication, meaning at least two studies, but we are certainly permitted under the law to approve a drug on the basis of a single study that we find to be so-called adequate and well-controlled, which is the language of the law.

So, it really does depend on the situation. We think there are certain significant issues related to some of these studies, but I think 1A is looking like a study

that is analyzable and interpretable. Some of the other studies I think have larger problems.

DR. GOLDSTEIN: When we begin our actual discussion that is exactly what we are going to need to come to grips with, whether the data that is available is sufficient to show efficacy. Dr. Temple?

DR. TEMPLE: We have a rule actually that defines what an adequate and well-controlled study is. It, itself, has considerable flexibility. For example, it doesn't say that all studies have to be blinded, but it does say you have to minimize bias. So, a question that arises is can you minimize bias if the study isn't blinded? Well, it depends on what bias you are talking about. So, an EEG read by somebody who doesn't know the treatment, you might think that solves the problem, whereas just the observer who is blinded in study 1A is certainly suspect and that might not be good enough but you might think the EEG is good enough.

It also says, interestingly, that if you didn't have the statistical plan in the protocol you have to tell us how you decided how to do the analysis. That is a level of flexibility probably not every statistician would be happy with but that is what the rule says.

So, as Rusty says, there is going to be judgment in all these things, and there is no question that flaws of a major or minor kind become affected in their importance by how strong the finding is. You know, you can't help but think that or, you know, how much we do what are called sensitivity analyses to see what happens if we make this assumption or that assumption. And, if a study survives those things you feel better about it.

In this case the fact that if you look at the EEGs that are outside the 3-day window you can think of that as the best analysis or as a sensitivity analysis, think of it any way you want. It sort of obviously adds strength to it because it doesn't seem to have a bias of a kind. But there is always judgment, as Rusty said.

DR. GOLDSTEIN: Three more questions and then break. Dr. Mizrahi?

DR. MIZRAHI: Thank you. I had two questions, primarily for the sponsor. One question is if some of the patients have a short-term response why is there a plan to continue long-term therapy? So, I think that is something. Or, do we know about relapse rates or whether there is a significant concern about relapse that the duration of

therapy is continued?

I guess related to that is a question, and perhaps this is an afternoon question, why is the focus on first-line application rather than therapy?

DR. SAGAR: In answer to your first question, the relapse rates in the three controlled studies I described were quite consistent, about 20 percent in all of the three studies. That is also true in the literature overall, that about 20 percent of vigabatrin-treated subjects relapse with continued treatment.

We have discussed before that there is not really rigorous scientific information about the appropriate duration of treatment with vigabatrin after spasm cessation has been achieved. The field is struggling with that issue. There is a follow-up study to the UKISS study that is currently being conducted in Britain right now, and they are using a 3-month treatment phase with vigabatrin with an initial vigabatrin plus steroid treatment phase. So, the field is trying to address the issue of appropriate duration of treatment but it is not resolved at this point.

DR. CUNNIFF: If I could answer the indication question, in the indication we have submitted to FDA in no

place do we say it is first-line therapy. It says it is indicated for monotherapy of patients with infantile spasms. I think, as Dr. Pellock and Dr. Shields say, that will be a clinical decision. There will be some patients where it is first line. There will be some patients where it is second or perhaps even third line.

DR. GOLDSTEIN: Dr. Gorman?

DR. GORMAN: I would like to ask Dr. Katz a follow-up question on Ait depends@ answers. Does the agency have any latitude when they are considering a therapy that is going to potentially be the first approved therapy for a catastrophic illness?

DR. KATZ: Well, I am not sure what you mean by possibility or leeway. What specifically do you have in mind?

DR. GORMAN: You used the Adepends@ word; it depends on the situation. So, in this situation there is no approved FDA therapy for this condition we are considering and we know it is a catastrophic condition. So, is that a parameter the agency wants us to take into consideration in our deliberations this afternoon?

DR. KATZ: The law, if I can retreat behind it, the

law says that you have to have substantial evidence of effectiveness, and it defines that in several different ways. Up until relatively recently it defined it as adequate and well-controlled clinical investigations, plural, which was typically interpreted to mean at least two studies. It is now a little while ago that the law was changed to say that substantial evidence of effectiveness can be defined as a single study plus something called confirmatory evidence, whatever that is.

We have sort of internal guidances about what sort of elements we would need to apply in order to say that a single study would suffice in the presence of something we could call confirmatory evidence. So, there is a standard in law but it is quite flexible and we can choose to apply the appropriate standard at the appropriate time.

DR. GOLDSTEIN: Dr. Temple?

DR. TEMPLE: In particular, there is nothing that says that studies can be a little cruddier. There is not anything like that. There is just one hint that some flexibility might be in order, and that is what is called our accelerated approval rule which was then endorsed in law.

What it says there is that for a very bad disease, especially a disease with no treatment, you can base approval on a surrogate endpoint that is some measure that isn't a clinical measure that you think is reasonably likely to predict benefit but isn't really well established to predict benefit. It is one area of flexibility.

For what it is worth, the very same ruleB-the rule, not the law-Balso allows us to base approval on an endpoint that isn't really the thing we want but is a clinical endpoint that is clinically meaningful. So, if you stop spasms early that meets the test for being a clinical endpoint, but what you really want is, you know, improved intelligence, things like that.

So, under such circumstances we can, but rarely ever have said as a condition of approval that we want to see a study that establishes those larger benefits, or a survival benefit in something where you are treating symptoms. But that is the one suggestion.

Now, the studies of this surrogate endpoint that isn't fully established, they still have to be adequate and well-controlled studies. There is no give really anywhere on that, though as Rusty says, you always have to make

judgements.

DR. GOLDSTEIN: And the last question before lunch, Dr. van Belle?

DR. VAN BELLE: I think I will defer until this afternoon.

DR. GOLDSTEIN: A wise response. Very good. Just a reminder for the committee, no discussions about anything related to what we are talking about. Lunch is in the same place as yesterday. There is no press conference this afternoon after the committee meeting is over. We will start again promptly at 1:00 p.m.

[Whereupon, the committee was recessed for lunch, to reconvene at 1:00 p.m.]

A F T E R N O O N P R O C E E D I N G S

Open Public Hearing

DR. GOLDSTEIN: This is the open public hearing portion of the meeting. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors. For example, this financial information may include the sponsor's payment for your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the

beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and its committee in their consideration of the issues before them.

That said, in many instances and for many topics there will be a variety of opinions. Our goal for today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by the Chair, and thank you for your cooperation.

Let me add just a couple of other things. One is that each speaker-Bwe have 15 I believe registered now, each speaker will be given three minutes. At one minute a yellow light goes on to let you know that you have a minute left. At the end of the three minutes a red light goes on and the mike goes off.

The other point is that, as I said, these are often very emotional issues for the public as well as for the committee. I ask the people in the audience to refrain

from applause, clapping or similar types of demonstrations. We need to be able to listen to everybody and listen to what they are saying. Dr. Ngo?

DR. NGO: Before we start I just want to let you know that if you received any inquiries from the public regarding the topic at hand, either yesterday or today, you are welcome to refer those questions to our press officer, Miss Sandy Walsh, and I will also email you her contact information and I will have it on the screen during our break as well.

DR. GOLDSTEIN: The FDA, for the committee, also has arranged travel back to the airport as soon as the meeting is over. Let me also remind the press that there is no press conference scheduled after the meeting today.

Let’s go on now to the open public hearing portion. The first speaker is Rachel Macri. Please forgive me if I butcher anybody’s name.

MS. MACRI: Hi, I am Rachel Macri. Thank you for allowing me today to speak about my son.

Philip is my second child of four. Luckily, I was not a first-time mom and understood that something was not right when at three and a half months he began having very

strange movements upon waking and falling asleep. He seemed despondent and not as playful as his brother, Peter.

On January 19, 2003 Philip was admitted to Scottish Rite Hospital and after a quick diagnosis we added two new phrases to our vocabulary, infantile spasms or IS and tuberous sclerosis complex. To add to the shock and distress we experienced on that fateful evening, we learned the only recommended treatment for IS was ACTH. We consented as we knew we had no other options, even if that meant we had to inject his tiny upper thigh twice daily.

Philip was discharged from the hospital and was still experiencing multiple seizure episodes lasting for several minutes, with 50-100 spasms each time. The seizures seemed to crescendo after a couple of days on the ACTH. We were terrified and there was another stay at the hospital.

After a few weeks the seizures did diminish but his sweet face started to change. Philip was 19 lbs. when diagnosed and just five short weeks later was close to 30. He also grew sideburns, a mustache and pubic hair.

What are we doing to our child was all we could think. We had countless doctor’s visits during his treatment to check his weight and for infection. His cheeks

became so distended that he was unable to smile. His limbs were so swollen that he could barely move. After a couple of weeks Philip's seizures had returned and we felt that our bubble had popped.

We contacted the TS Alliance and learned about vigabatrin. We were on a plane the next week to meet another neurologist and, after taking one look at him, she shook her head. We had spent so much time with him that we had gotten used to his disfigurement. Within the same time frame a stranger who we shared an elevator with felt compelled to leave a note on my windshield saying that she would pray for our family. Apparently, his appearance was very striking.

Immediately we all agreed that despite any of the risk factors associated with the use of vigabatrin we would try it. Simply put, terminating a seizure took priority over potential impairment of vision. We received the new medication shortly after our visit and we never saw another infantile spasms. Just like that, easily crushed and fed to him in applesauce, vigabatrin had cured his infantile spasms.

We were very lucky that we had the resources to

seek medical treatment a thousand miles away and afforded the out-of-pocket expenses associated with ordering vigabatrin from foreign countries. Because ACTH was, and still is, the first accepted line of defense in fighting IS Philip suffered with disastrous physical and emotional effects.

He is six years old and has yet to say his first words. We have only to wonder what his developmental state would be today if he had been treated right away with vigabatrin instead of the ACTH. I came here today, inspired by our sweet Philip and by the parents now struggling with babies and young children newly diagnosed with infantile spasms, to ask the FDA to please consider this very effective drug, vigabatrin, for people in the United States now. Thank you.

DR. GOLDSTEIN: Thank you. The second speaker is Karen Johnson-Wagner. I believe that she has some pictures that are being passed around the committee.

MS. JOHNSON-WENGER: Hello. My name is Karen Johnson-Wenger. My 16-month old daughter, Adeline, suffers from tuberous sclerosis and was diagnosed with infantile spasms at six months of age.

We brought home a beautiful baby girl who appeared perfectly normal and healthy. At two and a half months of age she began having repetitive movement in her left leg. She was referred to a pediatric neurologist. Before she could have a face-to-face appointment we needed to set up an EEG, which was abnormal, and then an MRI. After nearly four months we still had not seen a specialist.

During these months the movements continued to increase in frequency and intensity and began to involve both her legs and arms. Within four hours, Addie had 132 spasms in clusters of 20-25. Many times she would cry out for help but there was nothing we could do. We could not protect her or stop her from hurting. These few months do not seem long to us as adults but to Addie and our family it was half of her life.

Addie was developmentally on target until approximately three and a half months of age. At this time she stopped gaining and began to regress. She no longer held eye contact. She stopped smiling. She stopped laughing. She stopped reaching out for me. At times she could still roll over but she couldn’t sit up on her own. She began holding her eyes so wide that it was evident

something was wrong.

When she turned six months old she began showing more signs of diagnosable features of TSE. She was able to be seen in a clinic. After the MRI, it was discovered she has too many tubers to count in her brain and she was suffering from infantile spasms.

I am a licensed clinical social worker and have worked with kids for nearly 20 years. I only offer you my professional background to help you understand that the decision to allow Addie to begin taking vigabatrin was not taken lightly. We read and re-read everything and anything we could find on Internet. We spoke to people within the Alliance. There were numerous in-depth discussions regarding the benefits and side effects of this medication and our precious baby girl.

After taking the first dose of vigabatrin the infantile spasms stopped immediately. In a few days she began to smile. In a couple of weeks she began to laugh. She continues to progress developmentally where she is nearly age appropriate. When she smiles her whole face smiles and everyone’s day is brighter that is around her.

I want to read an excerpt from AWithin my Power@

by Forest Witcraft: One hundred years from now it will not matter what kind of car I drove, what kind of house I live in, how much money was in my bank account, nor what my clothes look like. But the world may be a better place because I was important in the life of my child.

We need your help. You can be important in the lives of our children and our families. Perhaps one day Addie and other children who suffer from infantile spasms will be able to stand right here and present to others because they have the ability to take vigabatrin and live a productive life.

By looking at the pictures that I have submitted, you can see how vigabatrin has helped bring Addie back to us. Thank you so much for taking the time and listening to our story.

DR. GOLDSTEIN: Thank you. Joyce Kramer?

MS. KRAMER: Hello. Joyce Kramer here, speaking for the Epilepsy Therapy Project. You have given me three minutes to help give 2,500 babies a year an opportunity for a productive life.

Let’s think about it. We have freedom of choice to balance between risks and benefits and, as I said

yesterday, we know from our web sites that parents look at a web site. They get information. Doctors get information. They are aware of the risks and benefits. Let's give them freedom of choice to make this risk/benefit balance and understand what would be available to them versus a non-approved drug in ACTH.

We also know that of the 2,500 children a year who develop infantile spasms, let's face it, you can give them vigabatrin now or you can give it to them later when they are adults and they have refractory partial epilepsy. So, based on your decision yesterday, let's back down in age and take care of these children right now.

We also know that ACTH is not easy to give. You saw some of the side effects from the first speaker. The hormonal treatment has severe side effects. We are not comparing it with a simple treatment. Vigabatrin does have problems with some visual field defects in 25 percent of people but it is effective. We know from the evidence that it works quickly.

I highly urge you to give open access for two weeks of treatment. Let parents try the drug to see if it works. Don't bother with ophthalmologic testing before you

give the drug. It is just not available adequately for people. In fact, the drug has been available only to upper class families who can afford to find the prescribers and import it from Europe. This is a class distinction that is so unfair when infantile spasms affects people without class distinction.

So, in summary, we know that the drug has been used elsewhere in the world. It is clearly in the minds of many families, and it is their choice, less dangerous than uncontrolled infantile spasms. Even if there are severe visual restrictions among children, that is still a life better than having Lennox-Gastaut syndrome or other types of refractory epilepsy.

We also know from some evidence presented this morning that children, even better than adults, can accommodate very nicely to visual restrictions when it occurs very young in life. So, you are not causing them great impairments compared to what else would happen.

Think about the societal perspective. Early intervention creates a productive individual long term versus lifelong need for physical, mental, social and medical treatment. I urge you to consider yourself as a

grandparent if your family came to you and said we have an infantile spasms baby, help us. What would you say if you decline this application today? Thank you very much.

DR. GOLDSTEIN: Thank you. Dr. Kossoff?

DR. KOSSOFF: Thank you for the opportunity to speak here today. My name is Eric Kossoff. I am a pediatric epileptologist from just up the street, in Baltimore, Maryland. I have no conflicts of interest to disclose. I am not an investigator in any Ovation studies.

I come here today on behalf of the Child Neurology Society. Dr. John Bodensteiner, the president of Child Neurology Society, asked me to speak today on their behalf. I represent CNS, which is 1,500 child neurologists in the country, that feels very strongly this is an issue that does affect both child neurologists as well as our patients.

Infantile spasms has been discussed here. It is, unfortunately, not a rare condition. We see it relatively regularly, about one new case every two months in our experience at Johns Hopkins, probably two or three times that in terms of refractory patients that we see. Many children have developmental delays.

In 2004, the AAN practice parameter, along with

the Child Neurology Society, felt that ACTH was probably effective based on the evidence, vigabatrin was possibly effective, and that was about it. Insufficient evidence for significant numbers of drugs out there but insufficient evidence.

It is a little hard to read here from the back. I apologize. If you look at clinicaltrials.gov, if you are child neurologist and you have a patient who is intractable and you want to refer them for another therapy, there is very little out there. There are basically three studies listed. All of these three studies are closed. Two studies on ganaxalone; one study, Dr. Shields was involved in which is completed, looking at surgery. All are closed.

Vigabatrin, as has been discussed, is a novel anticonvulsant, very widely used outside the United States for infantile spasms. This was a consensus survey that was done. Again, it is hard to read and I apologize, but in the United States ACTH was felt to be the most effective therapy in the opinion of pediatric epileptologists in the United States.

But there is a disconnect. In Europe vigabatrin is higher than ACTH and many of the other therapies. So,

there is a bit of a disconnect. And, you know, there is a lot of interest in the United States as to why there is a disconnect and can we get this drug.

In 2009, I can say it is nice to see so many other child neurologists, my colleagues, here today. Many child neurologists around the country are very interested in this topic, very interested in vigabatrin. Since 1994 there have been 809 human research studies about the drug with very interesting findingsB-tuberous sclerosis; there is the UKISS study, which was mentioned earlier today, looking at steroids alone versus steroids and vigabatrin; MRI changes; visual field data.

This is a drug that has not been in the United States for a while but people are very interested in it, hoping to get it available for use.

So, on behalf of the Child Neurology Society, I would strongly support new options for infantile spasms. Vigabatrin may be one of those options. We would like to have more tools in our armamentarium. It is nice to have those tools when very few are available today. Many child neurologists are very interested in this drug and the Child Neurology Society is very appreciative of the FDA for their

obviously very detailed and thorough review. Thank you.

DR. GOLDSTEIN: Thank you. Dr. Whittemore?

DR. WHITTEMORE: Good afternoon. First I would like to thank the FDA for allowing me to address the advisory committee today.

I am Vicki Whittemore, the vice president and chief scientific officer of the Tuberous Sclerosis Alliance. More importantly, I am an individual with tuberous sclerosis and the aunt of Clint, the wonderful young, 24-year old man up on the projector screen.

Clint was diagnosed with TS when he was three months old, in 1985. Like most infants who are diagnosed with TS, Clint was born after a normal pregnancy. He was a healthy, happy little boy until the day he started having his first single cluster of infantile spasms and then multiple clusters, leading to hundreds of seizures every day.

My sister and her husband knew something was terribly wrong, and he was quickly diagnosed with tuberous sclerosis and infantile spasms but for Clint that was the easy part. The difficult part was stopping the seizures. In fact, his infantile spasms were never stopped. The

treating physician had another child with tuberous sclerosis and infantile spasms who died while taking ACTH. So, because Clint had significant heart tumors associated with tuberous sclerosis, the cardiac rhabdomyomas, the decision was made not to treat with ACTH. The risk was just too great, a risk my sister and her husband were not willing to take.

So, Clint was started on the other medications that were available at the time, none of which ever stopped his infantile spasms. He went on to develop other types of seizures and today is a loving, gentle young man but he functions at the level of a two-year old. He is non-verbal, has autism spectrum disorder, severe intellectual disabilities and he will never live an independent life.

You will hear from the other parents today whose children face similar odds but, because they have the option of treating their child with vigabatrin, their children will have a much different outcome from my nephew. Since vigabatrin was first introduced as a treatment for infantile spasms children with TS have benefitted significantly from the ability to use this medication that in many cases stops infantile spasms after a single dose and sometimes after

only a few doses. A significant number of infants with TS who develop infantile spasms have the cardiac tumors and, therefore, ACTH is even more of a risk for them.

For most parents, a decision on what medication to treat their child with TS and infantile spasms is somewhat, as some would say, a no-brainer. Vigabatrin has made a significant impact on the future for children with tuberous sclerosis. On behalf of my nephew and all other individuals with tuberous sclerosis, I strongly recommend the approval of vigabatrin for the treatment of infantile spasms. The benefits that come from use of vigabatrin greatly outweigh the risks. Thank you very much.

DR. GOLDSTEIN: Thank you. Miss Kozisek?

MS. KOZISEK: Hi. My name is Laura Kozisek. My son Jackson was born in September, 2002. When he was three months old he began having seizures and was diagnosed with tuberous sclerosis. The seizures increased rapidly and numbered to around 15-20 per day with 20-30 clusters each time.

After each seizure Jackson would sleep. Because of the number of seizures and the required sleep Jackson was not able to develop like a typical kid. As a matter of

fact, he was digressing.

We were told that, because of his EEG, he was having infantile spasms and there were no medications that treated this type of seizure. We tried a variation of different cocktails with no reduction in seizures. He was on so many meds and he was having so many seizures that he was digressing in his skills. He was no longer able to walk safely across the room, play with toys or interact with adults.

At the age of two his development was that of a six-month old. He was not babbling. He had no eye contact and never smiled or laughed. A physician gave up hope on our son. Because of the different medications that we had tried with no success, we were told that our son would have seizures on a daily basis, would be severely developmentally delayed and would never progress.

As a mom I couldn’t give up hope. My husband and I searched out a new physician who prescribed vigabatrin and began weaning us off all of the other seizure meds. We were aware of the potential side effects but it didn’t matter. We wanted our son to have a quality of life that we didn’t have with all these seizures. We realized that he had a

chance to lose his peripheral vision but, again, it didn't matter. We just wanted our baby back. We realized that if he continued seizing at the current rate he would have no life at all. If he lost his peripheral vision but he stopped seizing he could learn.

After two weeks on the vigabatrin Jackson stopped seizing altogether. Two weeks after that he smiled for the first time and two weeks later he burst out laughing and he laughed for an hour. We didn't know if we would ever hear that beautiful sound. I am sorry.

He is now six years old. He has seizure management and he attends kindergarten. He is about two to three years age developmentally but he can swim; he can climb. He loves people. He writes his name. He plays with toys. He doesn't stop talking ever. He laughs all the time. He laughs with his brother. He laughs when we tickle him. And, he couldn't have accomplished this without vigabatrin.

In addition to our son, our nephew had infantile spasms. He was immediately put on vigabatrin and the seizures stopped. He has been given a chance to develop. We looked at the options and to us it wasn't an option. We

felt like we had to begin vigabatrin and get our baby back and to allow our nephew to develop. Please give our families this option. I am sorry. Thanks.

DR. GOLDSTEIN: Thank you. Ms. Anhang-Price?

MS. PRICE: Good afternoon, everyone. My name is Rebecca Anhang-Price. Thank you for giving me the opportunity to tell the story of my son Elijah's experience with vigabatrin. When Elijah was seven months old we traveled to California to introduce him to his great-grandpa. During that trip Elijah was irritable and had great trouble sleeping. He seemed to be startling himself awake several times in a row with sharp movements of his arms and cries in between.

A call to our pediatrician reassured us that Elijah just needed a sleep routine, but we found it alarming when, on the plane ride home, he startled several times then stared blankly off to the side for several minutes and fell into a deep sleep for two straight hours.

We videotaped the next startle episode to show to a neurologist. She examined the video closely and told us that it was an infantile spasm. She described the usual treatment, a strong steroid called ACTH, that we would have

to inject into Elijah every day, making him profoundly irritable, insatiably hungry and likely hypertensive.

Another neurologist offered us words of encouragement. She said some children with infantile spasms even go to kindergarten. My husband and I were in shock. Until that moment Elijah had been the picture of health and developing normally.

He was admitted immediately to the hospital for testing. An MRI revealed that his brain was riddled with tubers, the classic brain manifestations of tuberous sclerosis complex. The neurologist told us that while the diagnosis of TSE was not good news, at least now we knew the cause of his spasms and could begin to treat them with the most effective medicine available, vigabatrin.

The only means to get vigabatrin was through a pharmacy in Canada, however. We were told that prescription packages were often held up in customs for several days. We couldn’t imagine needing to wait to start treatment. In the eight days from when we noticed Elijah’s first infantile spasm to when he was diagnosed with TSE his spasms doubled in length and became more frequent. He became much less alert. He would not make eye contact. His primary mode of

speech was groaning. His muscle tone grew flabby.

We were lucky. My parents live in Canada and my dad filled the prescription for vigabatrin there and delivered it in person the next day. After only one dose Elijah stopped having infantile spasms. His alertness, eye contact and muscle tone returned within a few days. We felt that these changes in him were nothing short of a miracle.

Due to the potential side effects of vigabatrin on vision, Elijah is being followed closely by an ophthalmologist, and there is no question in our minds that the risk to Elijah's eyes is worth the benefit of the drug. Seven months since he started vigabatrin, our Elijah is an alert and smiling toddler who is developing without the constant disruption of seizures.

Elijah's health is not made perfect by vigabatrin. He is still at risk for other types of seizures, developmental delay, autism and many other medical problems. But with his infantile spasms under control with the help of vigabatrin we have hope that he will be one of those kids with infantile spasms who is lucky enough to go to kindergarten. Thank you for considering our story.

DR. GOLDSTEIN: Thank you. Ms. Krantz?

MS. KRANTZ: Good afternoon. My name is Robin Krantz. I would like to tell you about my 14-year old son, Noah, and our experience with vigabatrin. At 22 weeks into his gestation Noah was diagnosed with rhabdomyomas. We were told there was a relationship between those tumors and tuberous sclerosis. His heart tumors were so large the OR was on call at the time of his delivery as the team felt he may need immediate surgery. Amazingly, he did not.

However, the diagnosis of tuberous sclerosis was confirmed. At six months he began having infantile spasms. They went on for weeks, sudden, violent curling motions ending with a blood-curdling scream. He was irritable.

A neurologist at the time took four days to get him in for an EEG and three days to get back to us. It was tortuous. My baby was miserable and we were extremely concerned about the spasms as we knew there was a strong correlation between them and developmental delays. With each set of spasms we were imagining the IQ points decreasing. We also were concerned about the effects of the ACTH on his large heart tumors.

After a week of torture the neurologist told us he had to be hospitalized immediately for ACTH. We found a new

neurologist that afternoon. When he asked about the heart tumors he immediately suggested that we use vigabatrin. He reinforced the information about the effects of ACTH on the heart with rhabdomyomas and told us that vigabatrin had been used in Europe for many years with excellent results.

This provided an alternative to a treatment that could cause death. We carefully weighed our choices and quickly decided the risks were preferable to something that could kill our baby. We started the medication the next day. The seizures stopped immediately. Noah was on vigabatrin for five years.

Several years into his treatment we became aware of the reports about the relationship between the visual changes and the medication. We researched it as best we could. My father, an eye doctor, told us that in New York with peripheral vision loss you could pass the test for driving as that didn't test the field vision. We decided that without the benefits of vigabatrin Noah may not be able to write his name on the driver's test due to developmental problems. Thus, any decrease in visual field would be a moot point.

We did a careful risk/benefit analysis and it

became clear that the benefit to be seizure free outweighed the possible reduction in peripheral vision. Noah did not have any peripheral vision loss. He is now 14 years old, seizure free for eight years and seizure med free for five.

He is developmentally delayed. However, he goes to school, reads, participates in activities and recently celebrated his bar mitzvah. We feel that immediate seizure control gained by vigabatrin allowed Noah to keep as many IQ points as possible.

Vigabatrin provides a desperately needed option for those with tuberous sclerosis and infantile spasms. FDA approval is critical for these children. We need to be able to make informed choices. The children need access to treatment and insurance reimbursement. Thank you.

DR. GOLDSTEIN: Thank you. Ms. Dorman?

MS. DORMAN: Good afternoon. My name is Diane Dorman, vice president for public policy for the National Organization for Rare Disorders. Neither NORD nor I have any direct financial relationship or conflict of interest with the company in question.

I am here not on behalf of any pharmaceutical company but on behalf of the millions of men, women and

children affected by one of the 6,000 to 7,000 known rare diseases. Today there are nearly 330 orphan drugs and biologics approved for the treatment of rare diseases that treat, according to the Office of Orphan Product Development, somewhere between 11 and 14 million people in the United States.

Now, according to the National Institutes of Health, approximately 9-10 percent of the U.S. population are affected by one of those 6,000 to 7,000 known rare diseases. If you do the math, it could be said that well over 15 million Americas are left with no treatment specific for their rare disease. These millions of people can only hope that one day someone, somewhere will take on the significant financial risk to develop a therapy for them.

During negotiations of the FDA Amendments Act some argued there should be absolutely no conflict of interest for members of the advisory committees. NORD, along with some within the pediatric community, argued that by doing so would have a profound impact on the approval of orphan drugs, biologics and humanitarian devices. It is apparent, given the delay of review of the therapy for infantile spasms, this scenario has come to pass.

Because there are so few experts in the field of rare diseases and orphan drug development, conflicts will inevitably rise. Special consideration must be given to these products.

I am here today to remind the FDA and this committee that patients affected by rare diseases are willing to take a far greater degree of risk than those affected by more widely understood diseases affecting wider populations. Thank you.

DR. GOLDSTEIN: Thank you. Ms. Foltz?

MS. FOLTZ: Good afternoon. My name is Danielle Foltz. I am here on behalf of my son Trevor, who is joining us today via my slide presentation.

My son Trevor is now 21 months old and has been suffering from infantile spasms for over half of his young life. I appreciate this opportunity that you have given me to share my family's experience and the difficult decision that we have had to make regarding his treatment to cure his spasms.

Trevor first began having seizures at just seven months old. They were very mild but quickly escalated in both number and violence. Eventually we got to the point

where Trevor was having over 100 seizures a day. With guidance from our doctor, with put him on ACTH, for which we had to fight our insurance to cover, a battle which was hard won.

Yet, we had hope in ACTH. In fact, Trevor was seizure free after the fourth injection and remained seizure free for months. But as many of you are aware, ACTH is not a cure for infantile spasms and last September Trevor had a relapse and we have been dealing with that since.

We immediately tried a second round of ACTH which was unsuccessful. We then tried Zonegran which also was unsuccessful. After a lot of talking and debating and convincing, we finally convinced our neurologist to move forward with vigabatrin. She was very hesitant, not only because of the lack of FDA approval and the potential loss of the peripheral vision, she was also hesitant because of the time factor. Trevor was having 100 seizures a day.

Immediate treatment is essential. After much deliberation, my husband Jonathan and I, along with our doctor, decided that we must try vigabatrin. This is a stressful process on many levels. The ins and outs of using AEDs is never easy when you are talking about babies. It is

compounded by the red tape that a parent has to hack through in order to gain access to the drug.

It took us two weeks or 1,400 seizuresB-1,400 seizures--to get the box of vigabatrin in the mail and to start a trial. I wish that I could tell you today that Trevor was seizure free on vigabatrin. He is not. He has had a reduction. He is down from 100 seizures to 30.

But I am here today not to ask you to save just Trevor, I am here today to ask you to save all of these babies. We deserve a chance to rescue our kids. Thank you.

DR. GOLDSTEIN: Thank you. Dr. Thiele?

DR. THIELE: Hi. I am Elizabeth Thiele. I am a pediatric epileptologist, from Mass. General Hospital in Boston, and I am a consultant for Ovation Pharmaceuticals, and they did pay for my transportation and lodging for this meeting. But now I am actually representing the J. Kiffin Penry Epilepsy Program and many of my colleagues.

At the Mass. General I am director of the pediatric epilepsy program and also director of the Herscot program for tuberous sclerosis complex. So, I provide care to a large population of children with highly refractory seizure disorders, many of whom have infantile spasms. I

have now been using vigabatrin in the treatment of spasms for over ten years. If I do use it, like using other drugs for other seizure types, I do try to minimize the amount of time the child is on the drug, particularly if effective, I use it for a period of time and then try and taper the medication.

I now follow about 180 children who either have or have had infantile spasms. Similar to the other stories you have heard today, all of those children also have a story. Some have a story of doing very well, having their spasms quickly recognized, easily controlled. Some are now in college, in fact, one, a young man, with an IQ of 135.

A few of the kids while on treatment with vigabatrin had some interesting signal changes on MRI, and we thought this might be to why they were having infantile spasms. But those few children were then doing clinically very well, continued to and are now off drug.

Unfortunately, I also carry a large population of children who have very difficult to control spasms, many of whom have severe neurocognitive sequelae. All of those children have formed my experience with the role of vigabatrin in the treatment of infantile spasms. In

pediatric epileptology a lot of what we do every day is experience-based practice rather than evidence-based practice.

Also, I am here as a mother who can say I am very blessed that my children have never had infantile spasms, and I have never had to spend day and night worrying and praying that my child with spasms might look and recognize me as being their parent. I have never had to worry that my child might not be able to talk, comprehend or communicate with me; that my child might not be able to sit independently, walk independently or dress themselves; and I have never had to worry that my child is going through puberty will I still be changing their diapers.

Infantile spasms is a very devastating disorder but we know that some children can do very well, particularly if the spasms are quickly recognized and effectively treated. My colleagues and I really, really want vigabatrin and desperately need it as an available treatment option in the management of infantile spasms in all of our children. Thank you.

DR. GOLDSTEIN: Thank you. Mr. Zirkel?

MR. ZIRKEL: Thank you to the committee. I know

that you have heard from lots of experts and some amazing stories from parents here today, and you have seen some video and you have seen some pictures.

I would now ask you to really imagine being a parent yourself. Imagine holding your four-month in your arms. Without warning, his little body suddenly crunches up. For a split second you see the fear in his eyes, followed by the sharp cry of pain in his voice. He then relaxes because he doesn't understand that it is coming again. In 20, 30, 60 seconds another spasm is going to hit him, and with each one you know that there is not a damned thing that you can do about it. You know that these seizures are going to him several times a day, several clusters a day and all you can do is ask God to trade places.

About three years ago I got a frantic call from my wife saying that something is terribly wrong with our four-month old Jake. After a sleepless night in the hospital, we were told by the neurologist that he had infantile spasms. Over the next week we were told that it is likely that he will never walk, never talk, and be severely mentally retarded. No cause was ever determined with my son.

Within a week ACTH stopped the seizure clusters but they quickly relapsed and they became more frequent and violent. It got so bad that when the clusters didn't stop we had to give Jake Valium treatments to calm his whole body down. Four more weeks of increasing medication and no success resulted in the recommendation by his neurologist that we try vigabatrin.

Our dilemma? Risk of permanent vision damage for the chance to stop the immediate pain and long-term neurological damage. Our decision took all of two seconds. On December 14th, 2005 Jake received his first treatment of vigabatrin and from that moment until today he has been seizure free.

I would like to just take a look at my son Jake, who is right over there with my wife, so you can see a real, live success story of vigabatrin. Since that time Jake has been able to walk. He understands much of what we say and even speaks a few words like Amama@ and Adada.@ We can't imagine where he would be without vigabatrin.

We also try hard not to think about where Jake could have been had he taken vigabatrin at day one. He will always be developmentally disabled. He may never learn how

to use the bathroom on his own; have friends, as you and I would define that term; or even have a conversation with his older sister.

Your decision on this application will not make a difference in his life but it will have a profound impact on all of the infants who suffer through this horrible illness. Approving this medicine as soon as possible will increase recognition by the medical profession, get insurance coverage for the parents who desperately need it and, most importantly, give children as much, if not more, of a normal life than Jake has. Thank you very much for your consideration.

DR. GOLDSTEIN: Thank you. Dr. Buchalter?

DR. BUCHALTER: Good afternoon. I am Jeff Buchalter, director of the pediatric epilepsy program in Phoenix Children's Hospital. I would like to disclose that I am an investigator in an Ovation trial of clobazam for Lennox-Gastaut syndrome.

Dr. Thiele brought me back 20 years to a memory that I haven't thought about, how does a pediatric epileptologist do developmental milestones in their kids when you are beyond the age of infantile spasms? That is

how much terror it has for all of us.

I will now return to my prepared comments. I am here today as a pediatric neurologist and representative of the Epilepsy Foundation. The Epilepsy Foundation is a national organization that represents over three million Americans afflicted with epilepsy. I appreciate the opportunity to speak to you today about vigabatrin and the difficult decision before the panel regarding the FDA approval of the medication for infantile spasms.

The Epilepsy Foundation and I appreciate the FDA's essential role in assuring the safety and efficacy of the medications and devices for epilepsy. As a practicing pediatric neurologist, I want to assure my patients that the drugs I prescribe for them are the best possible products, with credible research backing up my statements.

That said, for families whose children are experiencing spasms we must also ensure that there are options available to them that come with FDA approval, even if that means serious side effects may be experienced. To put it in context, that is something we do every day. There isn't a day that goes by when I don't say to more than one family your child can die from being on this antiepileptic

drug. So, visual field loss is small in that context.

Children who are candidates for vigabatrin and their families are often in desperate situations. We recognize that vigabatrin has been very effective for some people but others consider it too risky due to the potential visual field loss. However, this is a decision that should be made by the family in consultation with their doctor, with risk/benefit ratio discussed.

For some people the decision is easy. Living with visual field impairment may be well worth the alternative of a devastating epilepsy syndrome, a catastrophic epilepsy with severe cognitive and physical disabilities and the risk of death. The reason that vigabatrin is often talked about as a first-line choice for spasms is because of its easy ability to rapidly escalate the dose, rapid efficacy and ease of treatment in the outpatient setting.

The Epilepsy Foundation is aware that families with children with spasms not controlled with ACTH, or sometimes with, are being forced to seek foreign markets to bring in the medication. There is a whole host of problems with this...

[Mike turned off]

DR. GOLDSTEIN: Sorry. Dr. Schachter?

DR. SCHACHTER: Thank you very much. I don't have a financial conflict of interest with the sponsor, nor did I have one yesterday when I spoke during the presentation yesterday.

I am here on behalf of the American Epilepsy Society, as its president, to speak in support of the approval of vigabatrin for the treatment of infantile spasms. I will, if you will excuse me, repeat a few points I made yesterday.

The American Epilepsy Society promotes research and education for professionals who take care of patients with epilepsy, study the causes and treatments of epilepsy, including infantile spasms. Our over 3,000 members include pediatric epileptologists, child neurologists who specialize in epilepsy, and we have very close working relationships with other professional groups such as the Child Neurology Society that we heard from earlier, the Academy of Neurology and the International League Against Epilepsy.

As we have heard throughout the day, West syndrome is a severe epilepsy syndrome associated with poor prognosis, significant morbidity and mortality. All

therapies currently available are off-label, and effective therapy improve developmental outcome and those benefits will last a lifetime. There remains a significant and urgent need for new therapies for infantile spasms.

Vigabatrin is an important new treatment option. Published clinical trial data support its use for infantile spasms, especially when associated with tuberous sclerosis. The potential side effects are well described and the substantial use of this drug in clinical practice outside the United States helps to inform the risk/benefit assessment, as well as the clinical approach to starting and stopping vigabatrin in patients with infantile spasms.

As we talked about yesterday, epilepsy clinicians choose these therapies by assessing the risks and benefits for individual patients, one at a time, based on available information about the therapies, their clinical experience and training and detailed knowledge of the individual patient’s neurological and medical condition.

Neurologists do this with individual patients and families, not on a population basis. As Dr. Buchalter just mentioned, we make these decisions every day involving therapies, including drugs or surgical interventions, that

could have life-threatening or life-altering side effects of complications.

So, in summary, new therapies for infantile spasms are urgently needed. Vigabatrin is an important new treatment option. Epilepsy clinicians individualize treatment decisions. American Epilepsy Society educates prescribers about the diagnosis of infantile spasms and the risks and benefits of treatment. And, I thank you very much for consideration of all these factors.

DR. GOLDSTEIN: Thank you. Ms. Wulick?

MS. WULICK: Hi. My name is Anna Wulick and I want to thank you so much for giving me a chance to talk to you about my daughter. Three years ago my daughter Laura was born with some odd pale skin spots on her thighs and her back. At 14 months old she was diagnosed with tuberous sclerosis but everything was fine until she was two, not only fine but her developmental assessment testing showed that she had the cognitive abilities of a four-year old and verbal abilities of about a three-year old.

At two years and two months she began having partial complex seizures which slowly increased until she was having 10 to 12 seizures a day. Our verbal, active,

happy, affectionate child was disappearing before our very eyes. She slowly stopped speaking. Eventually she stopped speaking entirely. She frequently did not recognize either me or her father when we came to get her after she had woken up from sleep. She began to regress more and more. She began to mouth objects; to completely stop perceiving her environment; stop responding to anything we said to her; and stopped understanding any external stimuli.

During this time we tried medication after medication which all failed her. Then we went as far as trying the severely restrictive ketogenic diet. Nothing helped. Then, finally, we found a new neurologist who prescribed vigabatrin.

From the very first dose she stopped having seizures and has not had a seizure since. Her EEG, which before showed nothing but epileptic and subclinical activity, is now normal. In the last two and a half months that she has been on vigabatrin she has regained every bit of verbal and cognitive skills that she has lost and now, in developmental testing she is almost indistinguishable from a normal three-year old, which is what we now hope to consider her, a normal child for the rest of her life.

But I often wonder how much of our life would have been different if she had been given vigabatrin as soon as her seizures started and we had not had to live through the horror of watching our child suffer and disappear before our eyes for almost a year.

I urge you to please consider approving this medication which would help so many suffering children and relieve the pain of their families. American children should have the same, if not better, access to children than children in other countries do. Thank you so much.

Panel Discussion/Questions

DR. GOLDSTEIN: Thank you. The open public hearing portion of the meeting is now completed. We will not longer be taking any comments from the audience. I would like to thank each one of the speakers for the time that they took to come here today to share their thoughts, their experiences and their perspectives. It is very, very important to the committee to have that perspective as well as the science.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments

that we have heard. As we said yesterday, these are the general sorts of issues that we are going to be addressing, the conditions, if any, that we think may be indicated; is there substantial evidence of effectiveness; the issue of the visual field deficit; has the sponsor identified a reliably sensitive monitoring scheme; and can or should the NDA be approved with the data at hand.

Can you bring up the other slide from the FDA? In general, these are some of the issues that the FDA has really asked us to focus in on as we discuss this. The first issue that we will deal with is efficacy in terms of the data that we have seen. Are these data sufficient in the committee's mind to show efficacy?

The second issue is the need for short versus longer-term therapy, which hasn't really been studied. The third issue is the safety issues that we have heard a lot about, the visual deficits as well as the intramyelinic edema, and the safety in terms of retinal toxicity.

So, if we can have the first question? Again as we did yesterday, we have a large number of questions and a large number of sub-questions that really precludes us voting on all of these things. What I would like to try to

do again is try to group them and, hopefully through discussion, address many of the sub-questions.

[Slide]

The first major one, and I have reworded it slightly from the way it appears in your packet, has the sponsor provided substantial evidence that vigabatrin is efficacious in the treatment of infantile spasms? Again, you know, when we say the sponsor we mean in the breadth of data that we have seen presented by the sponsor, the FDA and the other things in our packets. Can you bring up 2?

[Slide]

There are several sub-questions that actually come from this. It is listed as a separate question, each with a vote but, again, I think the discussion should encompass this. If we do feel that the studies show efficacy or don't, is it in terms of cessation of spasms, changes or improvements in EEG, the prevention of seizures in later life, or improvements in long-term developmental outcome? The answers, obviously, may be yes for some, no for others.

So, with that as a general background, I would like to open for the committee the discussion first about whether the evidence is sufficient to show that the drug is

efficacious for the treatment of infantile spasms with each of those sub-groups. Dr. Dure?

DR. DURE: It is more a point of clarification, is the word sufficient or substantial? It is substantial written down but you just said sufficient.

DR. GOLDSTEIN: Dr. Katz, you can help me here. I don't want to wordsmith this too much, but the idea is do we think the data isB-I guess sufficient would probably be a better adjective. But it is a legal definition and also the committee's view, but you can help us with the definition.

DR. KATZ: Yes, again, we have to by law determine that sponsor has submitted what is called substantial evidence of effectiveness. That is why we use that term. That is the legal standard. As I said before, you can think of it as sort of two different definitions of that.

Typically, it is defined as evidence from adequate and well-controlled clinical investigations. Of course, adequate and well-controlled, as we discussed before, would depend upon the circumstances and that sort of thing. But typically we require studies which provide independent replication or corroboration, usually two independent sources of evidence of two adequate and well-controlled

trials.

There is another standard which says that substantial evidence of effectiveness can consist of a single adequate and well-controlled trial. As you heard Dr. Temple say, the trials have to be considered to be adequate and well-controlled. So, one alternative definition is a single adequate and well-controlled definition and confirmatory evidence. It is not entirely clear what confirmatory evidence is or when this other standard is to apply, but it is certainly on the table as a standard that could be applied in this case, it seems to me.

So, that is why we said substantial evidence. It is a legal term. It is defined in the ways that I described, and that is what we would like you to think about.

DR. GOLDSTEIN: Dr. Temple?

DR. TEMPLE: We wrote a long guidance on some aspects of what confirmatory evidence might be, namely, when we might rely on a single study. Whether those apply here you have to think about but, for example, if there are other studies in a closely related disease that is sometimes considered sufficient to support reliance on a single study.

So, whether that case applies here or is relevant here is something the committee can think about. You know, there are other seizures. There are other documented studies in different seizure patterns. Whether that is relevant to infantile spasms or not is sort of a judgment that the committee might make if you think another study is needed.

DR. GOLDSTEIN: Dr. Repka?

DR. REPKA: Michael Repka. A couple of questions. Is it assumed by the pediatric neurologists that, in fact, the natural history of this disease over the two weeks before the primary endpoint is, in fact, essentially zero chance of regression given that the placebo in another study of the drug showed an almost 19 percent reduction in spasm frequency? That helps educate me.

Can this be differentiated by etiology? For instance, the data on tuberous sclerosis, at least on initial reading, looked more compelling to this reader.

And, I assume we are taking the two issues separately, that is, the 14-day or short course, whatever that really is after labeling, compared to a long course as separate issues?

DR. GOLDSTEIN: Well, let me let the pediatric neurologists on the panel first comment about your question. I guess it is directed at them. There was about a 20 percent or so reduction with the placebo. How often is that seen? Is that reasonable or not?

DR. CHUGANI: Harry Chugani. Yes, I think there are a number of kids who do outgrow their spasms. There is no question about that, but you never know how long it takes. On the other hand, there is data that shows that the longer one goes with intractable spasms, the worse the ultimate cognitive outcome is.

Having said that, it is generally accepted that even if you are able to control spasms with ACTH, vigabatrin or whatever, it does not guarantee a normal cognitive outcome. I have lots of kids in my practice who are totally controlled with vigabatrin or ACTH who continue to be developmentally abnormal, as the child we saw in the back. Even though you don't have any seizures you still are developmentally delayed.

But, certainly, one thing we do know is the longer the intractable spasms, the worse the cognitive outcome. The West syndrome is defined by the presence of

hypsarrhythmia on the EEG spasms, and then the third factor is developmental arrest. This is total arrest of any developmental progression.

DR. GOLDSTEIN: Dr. Repka?

DR. REPKA: let me follow that up. Are you then confident that the 16 percent response rate at 14 days is sufficiently different from what would be placebo or natural history, that this is indeed a drug effect?

DR. CHUGANI: Oh, yes, I think I am convinced. It is very rare for the spasms to resolve on their own. Sometimes it takes years, and we do see some kids when they are older, but usually that is beyond three, four, or five years of age when they sort of evolve into a different seizure type, sometimes atonic seizures, sometimes myoclonic seizures and no longer have spasms. I think this is a drug effect.

DR. GOLDSTEIN: I think the sponsor had a comment also to answer your question.

DR. SAGAR: Steve Sagar, from Ovation. I think you may be referring to the placebo group in study W019, and that was the placebo with a reduction in spasm frequency. It wasn’t an overall spasm cessation rate.

DR. GOLDSTEIN: And I think the other sub-question you had was whether this is equally efficacious across all seizure types. The only data I remember seeing was in CEI9 or CE19 from the sponsor. You may want to put that up and have them comment on that. I think that is the data that we saw about different potential etiologies. Dr. Weinstein?

DR. WEINSTEIN: It is probably irrelevant but the patients that are participating in these studies are patients that are going to major medical centers, both here and abroad. What is not clear to me is that a patient who doesn't make it to a major referral center, who is treated more locally necessarily has a better prognosis.

So, in my practice I get to see the worst of the worst. Of the 85 kids that I have seen with spasms over the last years, none has spontaneously stopped. Very few have responded to any medication.

Having said that, you know, the group that put these slides together and that were willing to participate in these studies had bad disease, and we may be asking too much to get a real handle on how efficacious this drug really is based on this subset of the population. So, we are looking at a subset here and, yes, it looks like kids

with TS perhaps do somewhat better but it does seem to work across all ages.

In the UKISS study, which is not presented here which did include the spasm kids, the drug seemed to be efficacious, equally efficacious between the two. As Dr. Hirtz pointed out, maybe there were some minor developmental changes in favor of ACTH but, again, these are not all-comers and these are patients that are participating in a study for whatever reason.

DR. GOLDSTEIN: I think the other piece of supportive evidence is from observational studies compared to what the natural history is. Obviously they are not controlled studies, but I think Dr. Katz had asked that question, given the reduction in infantile spasms at some later time point compared to what the natural history was, it seemed to be lower than would be expected. But, again, that is uncontrolled. Dr. Shields, I think you wanted to respond to that question also.

DR. SHIELDS: Don Shields, UCLA. Just one quick comment. Perhaps you are right but this is the only study I have ever done where I had child neurologists and pediatricians in the community calling me and asking me if

they could get their patients into the study. So, these were not just the patients who happened to wind up at UCLA; they were patients who came from all over southern California, Arizona and Nevada. So, you know, I think at least in our center this represented a pretty broad spectrum of the patients out there.

DR. GOLDSTEIN: So, I would interpret that means that you are underestimating the efficacy.

DR. WEINSTEIN: Well, no. Let's see, let me try it again, if you had all-comers and this is the real efficacy versus if it is a referral center you are underestimating the efficacy.

DR. SHIELDS: I think this represents the true efficacy. That is how I would look at it. These were patients from all over the place. As soon as they were recognized, people knew we were doing the study and were calling us and asking us to get the patients in.

DR. GOLDSTEIN: Dr. van Belle?

DR. VAN BELLE: Yesterday Dr. Cox mentioned--beside the criteria of two controlled clinical trials, he used the word ordinarily, and clearly we are not in an ordinary situation here. We are in an extraordinary situation. So,

then the question that comes to my mind is what do I look for when I look at these data when I try to come to some overall impression of the study?

And, one thing that I do, I tend to look at other variables, for example global scores, what do they look like. I look at potentially modifiable endpoints. We talked about that a little bit. I look at relapse rates, are they related to dose in some sense? That would be some kind of evidence. What is the history of the drug in other countries would be another issue.

The question that I asked earlier, is infantile spasm a subset of complex partial seizures, is important because that would give some evidence at least that it might be worthwhile to consider in infantile spasms treatments that have been approved for complex partial seizures.

I also look at the total population size. This is clearly a very small population. It is very unlikely that somebody is going to do a very large randomized clinical trial in this kind of population. Are there fatal flaws in all the studies that have been presented?

So, these are the kinds of criteria that I look for when I get into this extraordinary situation where we do

not have two randomized, well-controlled clinical trials.

DR. GOLDSTEIN: Thank you. Dr. Kieburtz?

DR. KIEBURTZ: Just to follow on those comments a little, I think we have a randomized study which has a blinded outcome assessor in 1A. I guess there is some concern about the multiple analyses and not controlling for spending of alpha in those analyses, but it strikes me that those analyses didn't have much impact on the conduct of the study and it probably makes sense that there is not a lot of spending of alpha in that regard.

Furthermore, the consistency of the response, just to get to some of Dr. van Belle's comments, across that study and across different analytic techniques, depending on which sort of chi square we are looking at the p value orbits around 0.05. I would argue that that is substantial evidence. That is the one study, and that FR03 is the confirmatory evidence, again, in a restricted population with a specific symptomatic TS as the cause of the infantile spasm. But I am having a hard time seeing why we haven't met the regulatory threshold for substantial evidence.

DR. GOLDSTEIN: I guess that is part of the discussion. Dr. Chugani?

DR. CHUGANI: Yes, I just wanted to add another point. We touched upon subgroups of patients where it might make sense to use vigabatrin and we talked about tuberous sclerosis as being the prototype of that. But I just wanted to put on the table several other groups of patients where it makes sense to use vigabatrin as the first medication.

It is well-known that children with three conditions, number one, neurofibromatosis; number two, premature kids, kids born prematurely; and number three, Down syndrome patients, these three subgroups, when they develop infantile spasms tend to be rather easily controlled either with vigabatrin or ACTH. Then the ultimate prognosis depends upon what their underlying condition is and infantile spasms does not add significantly to their ultimate prognosis.

But I can think of kids with Down syndrome and born prematurely where it would make no sense to use ACTH. For instance, in a child with Down syndrome and a cardiac defect you would not want to use ACTH. A child born prematurely who has bronchopulmonary dysplasia with lots of respiratory infections, those are very risky to use ACTH in. So, in those cases vigabatrin comes ahead of ACTH and we do

this all the time in practice. I just wanted to put that on the table.

DR. GOLDSTEIN: Thank you. Other general comments from the committee? Dr. Twyman?

DR. TWYMAN: Yes, I would just like to follow up on the earlier comments. I would like to submit that, you know, infantile spasms is a form of epilepsy. You know, if the data in the complex partial seizure group is substantial evidence that vigabatrin is an anticonvulsant, perhaps those two studies in the complex partial seizure groups provide substantial evidence and perhaps just a single additional study, like the 1A study here, could provide the additional data necessary for approval in infantile spasms.

An example like that is like it is for other anticonvulsants where partial onset seizures is approved and then additional indications are provided in Lennox-Gastaut syndrome with a single study and primary generalized tonoclonic seizures with a single study.

So, the question here is whether or not 1A provides substantial evidence, and I think, given the magnitude of effect and the low likelihood that complete clearance of all seizures and normalization of the EEGs is

so unlikely, that the magnitude of effect is probably real, and that you probably don't need to absolutely demonstrate this in a double-blind fashion. It is sort of like the parachute example. You don't need to do a double-blind study to try to identify whether or not a parachute helps save lives.

So, in this situation here I would like to try to submit that there is substantial evidence in the complex partial seizure group that this is an anticonvulsant and that infantile spasms is an extension of the indications in epilepsy, and that the single study 1A is sufficient.

DR. GOLDSTEIN: Thank you. Dr. Vega?

DR. VEGA: I am having a difficult time if, eventually there is approval, with the disparities that will be occurring because of the socioeconomic status. Only those people who have resources to get the medication will be able to get it.

I also don't understand yet how was it these other countries came to a consensus in terms of approving this medication. Does that mean the regulatory process is less strict than the regulatory process here, in the United States?

The other thing I am still not clear about is the duration of the therapy. Earlier it was said up to 12 months. I don't recall exactly. But it seems like there are children who have been taking this medication for many, many years. Is there a threshold where it begins, where it stops? I mean, I am not clear about those points yet.

DR. GOLDSTEIN: Thank you. Dr. Katz, Dr. Temple, I don't know whether you want to comment about regulatory approval elsewhere. We have to deal with what we have before us.

DR. TEMPLE: Right, we haven't really been asked to approve it until fairly recently so we couldn't have, for this. And, the fact that other people have it really can't be a profound influence. We have a legal standard to meet. There is a lot of judgment in it and the committee is being invited to make those judgments, but we still have to be able to say honestly that there is substantial evidence and effectiveness.

DR. GOLDSTEIN: And in terms of duration, I think we are going to be talking about that a little later. Dr. Lu?

DR. LU: Yes, in terms of supporting evidence, I

have a question about the W019 study that shows a reduction in the number of seizure frequency. I know that cessation is the key, but any reduction, does that predict the outcome of cessation and, you know, success with treatment?

DR. SHIELDS: Don Shields, UCLA. I think there are two ways to look at that. One is that reduction in seizures I think does demonstrate that there is efficacy. The issue of complete control is one of being able to improve the developmental outcome. So, that is our goal. In real life, if I have a child and I start them on vigabatrin and the child has a 90 percent reduction in spasms I am probably going to add something to try to see if I can get them over that last part before I bail out. So, I am not going to say this drug was not at all helpful; I am going to try to maybe add something to it.

So, there are two different ways to look at it. One is, yes, it is efficacious but not sufficient in that individual patient. I am still going on for 100 percent because that is what I need to do to give them a shot at development.

DR. LU: But do more frequent spasms predict a developmental outcome later on? Does anything correlate?

DR. SHIELDS: Well, I think the consensus of the community of child neurologists would be if you go from 100 to 5 you haven't changed the prognosis for development. You need to get to zero and you need to get the EEG out of that hypsarrhythmic state. They can still have seizures. That is a different issue.

Can I quickly address one other point? Would that be okay?

DR. GOLDSTEIN: Sure.

DR. SHIELDS: There was a question about complex partial seizures. Many of our patients do have focal lesions so you worry about the complex partial seizures having triggered the infantile spasms. So, you get the spasms stopped and you want to do something to keep them from having partial seizures that may fire off the spasms again during this developmental period.

Dr. Dulac, in France, at one time was putting the kids on *carbamazepine to prevent the partial seizures. All those kids relapsed and he just quit doing that. Many others in our experience have recognized that children who start with partial seizures may hasten their way into having infantile spasms by being treated for the partial seizures

with certain of our drugs. This is certainly not true of all drugs. If they were on a different drug it mightn't have happened. But it is recognized with carbamazepine and it might be true with barbiturates.

DR. LU: May I add more comments to that? Yes, I heard the testimony from professional associations and experienced neurologists about their practice. I understand that a lot of physicians practice based on experience, but here we should base more on evidence-based and there is always discipline we have to apply, regardless of, you know, how much we would like personal opinion.

I kind of struggle. I think from one side, you know, there are certain possibilities, not to say that definite bias exists there but possibilities like mentioned by FDA. On the other hand, if blind evaluation is the endpoint, that reduces some kind of bias. So, you know, as Dr. Temple earlier pointed out, if you look longer term, naturally it is in favor of efficacy. So, that weight was on the efficacious side. But on the other hand, the original endpoint was only marginal. I wouldn't say it is very convincing.

DR. GOLDSTEIN: What I would like to do is try to

back us into question 1, that I think we will take a formal vote on, by just addressing some of the sub-questions first. What I would like to do is start out with (d) and work our way back to (a).

So, do we think that the data that we have available shows a substantial improvement in long-term developmental outcome with the drug as opposed to not? First comments, and if there are no comments what I am going to do with each one of these things is just do it by consensus first. Yes, Dr. Temple?

DR. TEMPLE: I guess I have a question.

DR. GOLDSTEIN: Sure.

DR. TEMPLE: Oh, we are on (d). Sorry, never mind.

DR. KATZ: I do have a question.

DR. GOLDSTEIN: Sure.

DR. KATZ: This has to do with not the studies done with vigabatrin but the study that was discussed on slide 15. I think it was Dr. Sagar's slide 15, which is a study published in AEpilepsy@ in 2004. That is a study that purports to address the question of whether or not if you treat early you prevent the developmental delay. Could we have that slide? The Kivity study?

[Slide]

That is it, right. So, this isn't randomized or blinded, or anything as far as I can tell but, nonetheless, it purports to show that the kids who were treated early, all of them had normal outcome, presumably normal, and only 40 percent of the late treatments. Do we have any information about how that first group breaks out according to whether or not they were successfully treated, and what do we mean by success in this study?

DR. SHIELDS: Don Shields. As I recall, all of these patients were successfully treated. The early treatment patientsB-there was another sort of break point that I didn't put up there. One was how quickly were they treated and the second one was how far had they declined in their cognitive ability. And, 4 of the 6 in that late treatment category had gone longer than a month but had not really had major decline. So, it was sort of a combination of those two things but all of them were successfully treated.

DR. GOLDSTEIN: Thank you. Dr. Weinstein?

DR. WEINSTEIN: A point of clarification based on what Dr. Gorman has asked before, this drug is poised to

become the first drug that has an indication to treat spasms, which means that as a treating physician it becomes my first drug because the other one is clearly off-label. I guess the question is are there special hoops that a drug needs to go through when it becomes the only drug available that replaces the standard of care?

DR. TEMPLE: I mean, I guess you are asking whether early on we should have said you had better do a comparison with ACTH and show that you are better or, probably more interestingly, add it on and see if it does it. Well, we didn't do that.

Currently, it would be hard for us to say we know very much about what ACTH does, even though it is widely accepted. So, there is no special hoop. We tend to get excited when something treats something that has no approved indication so we have to control our excitement and make sure we get adequate data. That is the usual situation.

But, no, there are few rules about insisting on comparative data. You know, the world has become very interested in that and who knows what Congress might say and do but at the present time there isn't any requirement in our law that says you have to be better or even as good as

what is available. In the present case we really don't know that much about what ACTH does, not a lot of studies that have passed our muster anyway.

So, no, there isn't any particular requirement. But it is a question that the committee or we might consider, especially if there is some reason to think the old one was really way better. Then you are doing a disservice so we would worry about that.

DR. GOLDSTEIN: Dr. Mizrahi?

DR. MIZRAHI: Thank you. So, as we consider these questions, (b), (c), (d) and going up, in the absence of data specifically about vigabatrin we are actually being asked to extrapolate based upon other data, looking mostly at ACTH or prednisone, about whether or not long-term development actually improves with cessation of seizures, or there are fewer associated seizure types after spasms are resolved, or that the EEG improves. Because it seems that the endpoints that we have been looking at here with these specific studies have really been seizure cessation.

But, you know, I wanted to raise the point just to be certain that I am not missing it and that there has been data that either has been presented or has been part of

these studies that we have been discussing that haven't really been brought to the forefront. If somebody could speak to that.

DR. GOLDSTEIN: Dr. Katz?

DR. KATZ: Maybe you can think of this as sort of two parts. I think we were primarily interested in whether or not you thought there was evidence that vigabatrin improves long-term developmental outcome. So, that is sort of the first, is there evidence specifically with regard to vigabatrin on this question.

I suppose you could offer a view that even if you think that there is no evidence specifically related to vigabatrin on this question, there is so much evidence out there that no matter what you do to stop the spasms, if you stop them you improve developmental outcome.

I suppose you could sort of at least give us your opinion about whether or not you can generalize from that data to say, well, there is no specific data with vigabatrin but vigabatrin stops the spasms and, therefore, it must, or we think it does or will prevent the developmentalB-so, it would be interesting to hear what you think about that, though I think we are specifically first interested in

whether or not you thought there was specifically evidence for vigabatrin on this question.

DR. GOLDSTEIN: Dr. Hirtz?

DR. HIRTZ: So, we have not heard about it today probably mainly because it was considered class IV evidence, but I would like to read to you what was stated in the practice parameter, which is the evidence review, about specifically this question, and that is that there were two class IV studies which related to long-term outcome after vigabatrin.

So, one of them, 17 percent of the children were normal or slightly developmentally delayed and 72 percent were seizure free for at least a year. That was one study, again, class IV, prospective observational study, not randomized.

The other one, 36 percent of children were seizure free and developmentally normal. They compared 90 percent of the cryptogenic patients who had a good outcome compared with-Bthis is a small study so 9 of the cryptogenic patients and one of the symptomatic patients did well. They were followed from between 10 months to 3 years.

Now, the only other evidence that I am aware of in

terms of long-term vigabatrin is going to come from the UKISS study which has both ACTH and vigabatrin and will be published soon at about four years after follow up. I understand that both show not full but definitely developmental gain.

DR. GOLDSTEIN: So, the way that I was interpreting what you are asking for here is two different things. One is the discussion we are just having for you, and that is if seizure is controlled would we expect, or would people expect then there to be improvements in developmental outcome.

The second part, and the thing that we are actually trying to hone in on, is of the data that we have seen here is there evidence of substantial benefit in these outcomes as you defined it. So, it is two separate but related questions. One we are having the discussion about, the other thing is that we are going to try to get votes on. Dr. Kramer?

DR. KRAMER: Actually, my question was answered.

DR. GOLDSTEIN: Thank you. Dr. Jensen?

DR. JENSEN: Yes, given what Dr. Hirtz just told us, is that admissible in our decision-making process since

there seems to be prepublication information about this very question?

DR. HIRTZ: I mean, I think they have already published shorter-term follow up of 14 months. I don't have specifics on the longer.

DR. GOLDSTEIN: Remember the definition of substantial that was given to us. These are class IV observational, uncontrolled studies so, again, we may say that it seems reasonable but that may not be substantial based on that definition. Dr. Chugani?

DR. CHUGANI: I totally agree with what I have heard said and am familiar with those studies. Again, I think the consensus is that if you get your spasms controlled you will probably do better cognitively. But also we have to point out that it doesn't guarantee you that you will have normal development. That is the point I wanted to bring out.

So, there still are lots of kids who are controlled and they haven't had spasms in years but they are not cognitively normal. Specifically, some patients will not develop no matter how well controlled they are. But the general feeling is that, yes, if you get them controlled

they do better cognitively.

DR. GOLDSTEIN: So, I think just to try to bring this issue to some closure, I think hopefully, you have a sense of the discussion that the experts that take care of these folks think that if you control seizures they would, hopefully, expect improvement in developmental outcome but that may or may not occur.

In terms of the specific thing, does the data in hand show substantial improvement in developmental outcome with treatment versus not, I think we have discussed it enough. I would like to just get, again, a consensus on it and then we will move on to the next. Who feels that the answer to that question is yes? Dr. Weinstein, point of order?

DR. WEINSTEIN: You said with treatment.

DR. GOLDSTEIN: Yes.

DR. WEINSTEIN: Treatment with this specific drug?

DR. GOLDSTEIN: Yes, with this specific drug, absolutely, because what we are trying to do is back us into the first question. For example, if the answer is yes for any one of these sub-questions, or it looks that way, then that backs us into the answer to the first question. Yes,

Dr. Kramer?

DR. KRAMER: I have a clarification on the process we are taking here. It seems to me a little bit backwards to be backing into the first question. It seems to me that the usual way you do it is, is there substantial evidence of efficacy by whatever measure the sponsor has presented, and these are subset questions--

DR. GOLDSTEIN: Right.

DR. KRAMER: You could have an opinion about them from observational data, experience, whatever but the subset questions may not require the same two studies with substantial evidence of long-term developmental outcome. Aren't we doing it backwards?

DR. GOLDSTEIN: That is exactly right. That is why we are doing two things. We are having a discussion and then we are trying to address the specific definition that the FDA has asked us to address about substantial evidence for each one of these. It may be no for all of these and then we may come to the first question and decide yes.

DR. KRAMER: Well, that is not what I am saying. What I am saying is do we have to address the question about substantial evidence for each of these?

DR. GOLDSTEIN: I am going to do it but not in a specificB-I want the FDA to have a sense of what the committee's opinion is about the data that we have seen, but that is not binding on the answer to the first question. Okay?

So, we are having the general discussion first about what the committee's view of the available data is; what they think based on their expert opinions, whatever our expert opinions may be; and then the specific thing based on the formal definition of substantial evidence for each one of these; and then finally the first question.

Any other clarifications? Does this seem reasonable to people? I am just trying to give the FDA what they have asked us to give them. Dr. Vega?

DR. VEGA: This is just a clarification on (c), for the prevention of other seizures types later in life, what do we mean? From childhood to adulthood or from childhood to--?

DR. GOLDSTEIN: Let's deal with (d) first then we will do the next one. So, the first one is the improvement in long-term developmental outcome. We had the general discussion about how people have felt about it. Now in

terms of the formal definition of substantial evidence for efficacy in terms of improvement in developmental outcome based on the data that we have seen. Yes? No? Abstain? So, it is somewhere between no and abstain as a general sense. Okay?

Now let's deal with the next one, prevention of other seizure types later in life. We have seen some data for this and we have heard, again, discussions from experts that if you can control the infantile spasms there may be a reduction in later life seizures. Open first for comments and discussion. Dr. Vega?

DR. VEGA: Well, again, what do we mean by later on in life? When they become adults?

DR. GOLDSTEIN: I am happy to entertain any definition of later in life. I assume it means outside of the immediate childhood period. Dr. Chugani?

DR. CHUGANI: As a person who deals a lot with kids with infantile spasms, I have never heard that. I am just wondering where this came from, that if you stop the spasms you would have eventually a reduction in some other type of seizure. I never heard that before. Have you?

DR. GOLDSTEIN: Dr. Katz?

DR. KATZ: We are just asking the question. Again, it is sort of under the heading of does it prevent subsequent complications of the infantile spasms syndrome. In other words, these kids go on to have other seizure types, just as they go on to have developmental delay. The question is does this drug treat any of that or does it just treat the spasms?

DR. CHUGANI: Yes, I think we have zero handle on that one.

DR. GOLDSTEIN: Dr. Dure?

DR. DURE: Yes, I mean, Dr. Goldstein, you had mentioned that we have heard evidence about that today and I just don't recall any evidence suggesting that. I guess the point is that this seems likeB-well, again, I share Dr. Chugani's concern. I mean, I am not sure why this is here. Is this a bar that the FDA wants it to meet, or do you just want information?

DR. KATZ: We are just trying to figure out what you think the drug does, or has been shown to do. Infantile spasms is associated with many other complications. The question is do you think that vigabatrin treats the spasms? Do you think it treats these other seizure types? Does it

treat the developmental delay or prevent it even? That is what we are trying to get at. We are not presupposing it does any of these things. We just want to get your views about what you think it does.

DR. GOLDSTEIN: There was some discussion—we didn't see data about it—about the potential for affecting later seizures. I think that is where it came from. Dr. Weinstein?

DR. WEINSTEIN: You just mixed apples and oranges. You said prevent subsequent seizures versus treat other seizures. We yesterday voted that it treats other seizures but the idea of prevention, of preventing epileptogenesis or going on and developing predisposition, I don't know that I have heard any evidence for that.

DR. TEMPLE: We are not saying you heard any evidence, but there is a view, for example, that treating the spasms prevents the developmental abnormalities later. Okay? So, what he is asking is, is there evidence that some of these seizures that supervene later might also be prevented. We are not advocating that position. It is just a question. And, the answer might be you don't think there is any evidence. That is fine.

DR. GOLDSTEIN: Dr. Dure?

DR. DURE: This presupposes that we actually understand the pathophysiology and pathogenesis of this constellation. I mean, you are saying associated but I don't know if I could say confidently that one always follows another for a specific reason. There are children without tuberous sclerosis who don't develop developmental delays and those with tuberous sclerosis who do. I mean, to assume that these mechanisms are similar I think is a bit of a leap. I would like to know if I am off base on that.

DR. KATZ: Well, let me again just try to clarify. We are not assuming anything. We just want to know what you think about this. We are not assuming that this drug will do this or anything else. We just want to know whether or not you think there is any evidence that this drug treats all aspects of the infantile spasms spectrum or just the spasms. That is all.

DR. GOLDSTEIN: Dr. Hirtz?

DR. HIRTZ: Now I am confused. I just need some information. What I hear Dr. Goldstein saying is that we should answer the questions based on the evidence that was presented in the two presentations this morning basically

about the three studies that are class I or II studies. The way Dr. Katz is phrasing the question is what do you think based on this plus other studies plus our general knowledge, and I would just like to know how to answer these questions.

DR. KATZ: We would prefer you to answer based on the evidence you have seen presented today for vigabatrin or in the application.

DR. GOLDSTEIN: What I think we are doing is two things. One is this discussion we are having now, which is what people feel based on every piece of knowledge that you have. The second thing is, is there substantial evidence presented from what we have seen. They have no preconceived answers to these questions. They want to know what we think about what we saw and then also what we think based on your professional experience and other data you may have. Dr. Temple?

DR. TEMPLE: Well, in retrospect I probably wish we had left those questions out, but the reason they are there is obvious from the public statements that we heard. Many people involved in this disease in the most important way plainly believe that some of these benefits accrued because of the treatment. And, that may, indeed, be true but to

explore whether you think there is enough evidence to say anything about that now was the purpose of those two questions. You know, we don't think there are a lot of controlled trials that show it either.

DR. CHUGANI: Yes, I think I can clarify that part of that. I think the developmental delay of a child with infantile spasms probably comes from two different factors, the first of which is the underlying cause for the spasms, which we know. In infantile spasms most of it is some malformation in the brain, some cortical dysgenesis. Now, that alone, even without seizures, can give you developmental delay.

Then that child develops infantile spasms which totally arrest the child's development. It is that component that you can treat and when the seizures are stopped that component will be off the table then. You are still left with the underlying etiology which most of the time is going to be some dysgenesis in the brain.

That is why I say you can't guarantee ultimate outcome. It depends what the ultimate pathology is of those patients. So, the answer is yes and no. Yes, you can reverse but, depending upon the etiology, how much can you

reverse?

DR. TEMPLE: But still you have sort of answered the question to say oh, yes, I know the part of it that was due to the spasms is going to be reversed by treating the spasms. It would be hard to identify any controlled trials that showed that. But that is why Rusty put the question. You know, there are belief systems and there is also data. Those are not always similar.

DR. GOLDSTEIN: Right, and we are doing both, the belief system and the data. So, I think, hopefully, we are past the (d); we are onto the (c). I think we have had a discussion, I hope, first, about what the general impression was that I hope you have had and then the actual question is, is there substantial evidence that treatment reduces or prevents other types of seizures in later life? Is there substantial evidence from what we have seen showing that treatment with the drug prevents seizures in later life? Yes?

DR. WEINSTEIN: Are you talking about epileptogenesis or somebody is going on and going to have seizures and we are treating their seizures by leaving them on vigabatrin?

DR. GOLDSTEIN: It is prevention of other seizures in later life. So, my interpretation of that is that you treat with the drug, then at later life they do or do not go on to other seizure types. Have we seen evidence for that? That is what the question says, prevention of seizure types, other seizure types in later life. Dr. Kramer?

DR. KRAMER: I think we are making this too difficult. I think we can just take this very literally--

DR. GOLDSTEIN: That is what we are trying to do.

DR. KRAMER: I mean, the question that is not on the page is if we consider that vigabatrin had substantial evidence of efficacy, for whatever reason, do you think that there are data themselves to show that there is prevention of other seizure types later in life, assuming you use it in the first place. Just yes or no. You can say no and then you can say what you think your experience would indicate. But it is asking about the data.

DR. WEINSTEIN: But we voted on it yesterday to say it is efficacious in preventing seizures.

DR. GOLDSTEIN: First let’s take yesterday off the table. Yesterday was, was it efficacious in treatment of patients with partial complex seizures who were refractory

to several other drugs. What we are asking here now is if you take a child with infantile spasms and you treat them do you prevent the development of other seizure types in later life? Is there substantial evidence to show that or not? Take it literally.

DR. KRAMER: Be very concrete.

DR. GOLDSTEIN: Yes? No? Abstain? Cool. You have our sense.

Next, we have seen data about improvement in EEG and that came from randomized trials, or a randomized trial and other data as well. So, first the general discussion. Is there an effect of the drug, do you think, on improving the EEG? Comments? You have to be kidding! Okay, let's take it literally. Dr. Mizrahi?

DR. MIZRAHI: I do think that there was information in the studies to suggest that the EEG does change with therapy because part of that was not only part of the outcome, was not only seizure cessation by parental observation but actually going a step further and looking at EEG and then EEG video monitoring to make that confirmation.

So, in fact, in this particular instance I think there is evidence to suggest that. Now, whether or not it

rises to the standard that we might be legally bound I think is a different issue.

DR. GOLDSTEIN: Can you put up Dr. Sheridan's slide 14? That is about the simplest one for us to just have up there. So, that is sort of a summary for the best data. Now, remember their stricter definition as I remember it, correct me if I am wrong, included normalization of the EEG.

DR. MIZRAHI: I am not so sure it was normalization of the EEG as much as it was no longer being hypsarrhythmic.

DR. GOLDSTEIN: I am sorry, you are absolutely right. That was the definition. There is the data from those studies. We heard about other data as well. Dr. Temple?

DR. TEMPLE: It is worth remembering that those data do not include the analyses that allow you to look at the EEG more than three days afterward. You know, people will have varying views on that but the nominal significance becomes considerably more extreme when you do that. So, you have to decide whether that in some way is a distortion or an intelligent adaptation to discovering that you can't get EEGs very fast.

DR. GOLDSTEIN: Do you guys remember what slide

number that was?

[Slide]

There we go. So, we have the data from the randomized trial that we saw that included amelioration of the EEG. Then we have those data as well. So, the question is does that reach the level of substantial evidence or evidence of substantial effect of the drug on amelioration of the EEG? Let's bring that to a question. I think it has been adequately discussed. We have all known and seen the data. So, let's tryB-Dr. Kramer?

DR. KRAMER: I wanted to ask this morning but I didn't have time, but in the design of study 1A, could somebody just clarify for me, it is randomized to high dose and low dose but there is a range of high dose and a range of low dose so could somebody clarify how the dose was chosen?

DR. SAGAR: The dose ranges which appear so strange were due to the investigators being given 500 mg pills and, by calculating what they expected, the range of weights was going to be in a typical population of IS subjects and in designing a high dose and low dose they basically had to use multiples of 125 mg.

DR. GOLDSTEIN: Any other comments? So, let's try it and see what happens. Is there substantial evidence, as defined, that treatment with the drug ameliorates the EEG in children with infantile spasms? Yes? No? You have our sense.

The last question, letter (a) under this is, is there evidence or substantial evidence that treatment leads to a cessation of spasms? Again, the test that we are looking for eventually is substantial evidence as defined, but also I think we have heard a lot of discussions from both the public and societies from the open public hearing session about their opinions about this, as well as some of the committee members just in general. Any other general comments first? Yes, Mr. Bartenhagen?

MR. BARTENHAGEN: Just a few quick comments. I am here not because I have Adoctor@ before my name; underneath my name the only thing you read is Nebraska, but I do have a son that is seven years old who was diagnosed with infantile spasms in 2002, which has since progressed to Lennox-Gastaut syndrome. He has 50 to 100 seizures a day. I am sure by this time today he has gone through 50 seizures, and has for seven years.

I know what doctors like to do is discuss numbers, and I have heard a lot of it. I have to admit I have had to lean over to Dr. Twyman a few times and ask some questions about what some words meant. But it certainly appears to me that with all the pediatric neurologists, I haven't heard one say that they have any doubts that this can help people. I haven't heard that mentioned once. And, I sure think that the bar for efficacy needs to be considered.

I don't know if I understood Dr. Temple right, and I am going to paraphrase it, but it seemed to me like he said there was a provision for close enough, not perfect but close enough. No?

In my opinion, the decision that is being made today my wife and I made. I don't remember if it was in the car on the way to a basketball game or at the kitchen table. We talked about everything that was talked about here. You know, not with the PowerPoint presentations, not with the lights and the cameras, but we made the same decision and, unfortunately, it didn't work for my son but I am glad we had the opportunity. And, I think it would be a shame that because it doesn't work for 17 percent of the kids or 18 percent of the kids or 19 that those 16 percent that it

worked for don't get the opportunity to use it.

DR. GOLDSTEIN: Thank you. I think we have had a thorough discussion of what people's opinions are. Let's hit the actual question, have the studies that we have seen today provide substantial evidence of efficacy in the cessation of spasms? Again, this is the consensus part and then we will go on to the actual vote part in a sec. Yes? No? Cool, you have our sense.

Now let's go to question 1. I said we would be backing into this. First, any general comments? Wow! So, now what we need to do is we need to do the formal vote. Has the sponsor provided substantial evidence that vigabatrin is efficacious in the treatment of infantile spasms?

Having gone through everybody's opinions and their experience, as well as the data that we have seen, the test here though is based on the data that we have seen. So, press your buttons. They tell me that the buttons for voting should work even though the microphones don't. So, press your buttons.

[Electronic voting]

DR. GOLDSTEIN: Now we have to do the formal roll

call. She tells me we don't have to do it into the record. It is unanimous. She will just say it into the record.

DR. NGO: We have 25 yes; zero no; and zero abstentions for 25 votes.

DR. GOLDSTEIN: Very good. According to my schedule, we are scheduled for a break at 3:00. So, I think this is a good time to do it. Let's take our 15 minutes for biology. We will come back, instead of 3:15, at 3:10.

[Brief recess]

DR. GOLDSTEIN: If it is the committee's pleasure, what I would like to do is change the order a little bit and try to combine things to try to attack multiple issues semi-simultaneously. We talked about the efficacy. What I would like to do is switch now and let's address the toxicity issues next and we will take it from there. Dr. Ngo has an announcement first.

DR. NGO: For the panel members, we will be having some shuttles available for you from the hotel at the end of the meeting. Unless you are leaving a little bit early, the rest of you will have a shuttle that is going to go directly to your destination. It is going to be paid by us so you don't have to worry about payment when you get to the

airport but maybe just a nice gratuity. Also, Dr. Larry Schmued, if you are still watching us on the web, please dial in. Thank you.

DR. GOLDSTEIN: Thank you. In terms of the toxicity, what I think I would like to try to do first is try to deal with the visual issues which are your set of questions 4(a) through (g) and question 5. What I would like to do is try to package those and sort of talk about all of those together.

One thing that I would just like to start off the discussion with is-BI think this is probably best summarized in the sponsor's slide CII-9. Can you see if you can find that one? Do you have that? It was on page 5.

[Slide]

There we go. You know, we heard a lot about the difficulty in assessing vision in these very young children that may have other issues. But I think from what we heard, the incidence seemed to be about 31 percent, with the literature range between 17 and 92 percent. We had a long discussion about ERGs and the issues or ERGs. Again, from what I heard, it doesn't sound that that is a practical, usable method of monitoring children that is practical from

any standpoint.

The measurements are clinically based and it is based on the best assessment of neurologists and possibly ophthalmologists that are caring for these children. There are large issues related to the sensitivity of those assessments. We didn't hear much about central visual loss. I don't know that we could say whether that is affected or not affected.

But just based upon this, the way that I would at least propose to summarize all of this is that visual deficits may occur or are likely to occur. They could be severe. They could be irreversible. And, there isn't a clinical monitoring way of assuring anybody that it could be caught at an early stage.

The sub-question that I hadB-again, maybe the sponsor or some committee members might have is, are there any data about long-term vision in kids that have been treated with this drug early on for infantile spasms? We had a lot of observational data, a lot of it experience, although I don't know that we have substantial data from any of these trials. Let me just open that up first and then see if we can open up, obviously, to comments by the

committee. Dr. Vega?

DR. VEGA: It seems to me, and correct me if I am wrong, that these children, because of their conditions, either TS or something else, without the medication, let's say, they will eventually have a lot of additional problems without medication.

DR. GOLDSTEIN: Well, we have a number of pediatric neurologists here that take care of kids with tuberous sclerosis and infantile spasms. What is the incidence of peripheral visual loss or central visual loss in those children? Do we know? We may not know.

DR. CHUGANI: It is higher than the normal population but it depends upon the underlying pathology. I mean, if there is cortical dysplasia in patients with spasms and it affects your occipital-temporal region you are going to get some field cut. You can have other visual disturbances. Certainly with tuberous sclerosis patients, they can have tumors in the eye and they can be affected as well. But I don't think that you can make a statement generally that they will develop visual problems. They may or may not.

DR. GOLDSTEIN: Dr. West?

DR. WEST: I think that visual problems is such a vague term, visual problems could mean anything from needing glasses to being cortically blind, or central visual impairment as is the preferred term these days. But children with neurologic impairment and seizure disorders do have a higher rate of what is considered more than needing glasses. They have a higher rate of amblyopia and strabismus. They may have central visual impairment if there are structural abnormalities of the brain. Children with TS can also have central visual impairment from their central lesions but could also have impairment due to hematoma in the papillomacular bundle, which is the central part of the visual area of the retina.

So, many of these children are being seen regularly for a variety of vision and eye problems that can affect them. Then, there are going to be some of the children who have underlying neurologic or metabolic diseases that have cortical or central visual impairment.

DR. GOLDSTEIN: Okay. Other general comments? Anything specifically? I think, you know, we heard a lot about the ERGs. I don’t think anybody is proposing that this is a practical method for use in this population,

certainly not on a nationwide basis. Dr. Kieburtz?

DR. KIEBURTZ: I was just going to recapitulate. Are we in the general comment area?

DR. GOLDSTEIN: Sure.

DR. KIEBURTZ: It seems like there is not going to be any screening test which is going to be able to identify damage before it is clinically apparent that is readily feasible. So, I think the assumption could be that children that are treated with this are going to have the probability, or the possibility and in all likelihood the reality of encountering significant visual impairment that won't be identified until it has happened; that is irreversible and may progress some even after the time it has happened. We don't know that for sure.

That is the lay of the land, and I don't think it is feasible to require the sponsor to come up with a screening test that is going to beat that. I think that is the risk that is going to be managed and is being managed now with its use, probably less well than it would be through the REMS in my opinion.

But I think we have to offset-Bin some of the very eloquent and courageous discussion we heard from the public,

I think people would certainly trade that for seizure freedom. But I think as we heard from our colleague on the panel, it may be that you are going to trade that for no clinical benefit too. You may end up with a visual impairment and have no benefit from the drug. Is that still a reasonable thing for people to make an informed decision about? I would say yes but I think it is something that is worthy of us talking about because I don't think we are going to have a screening test that is going to prevent it from happening. It is going to happen.

DR. GOLDSTEIN: Mr. Bartenhagen?

MR. BARTENHAGEN: I will say in our own situation we put Brock on Sabril with the intentionB-we did not do any baseline tests or anything, but our tolerance for vision loss was going to be much higher if it controlled the seizures. I mean, if we went from 100 seizures a day to zero our tolerance on what we could accept for vision loss would be much higher.

I think, at least in the area where I live and we saw pediatric neuro-ophthalmologists, you know, the standard practice was we make a three-month or six-month trial at that time for having success. We do a test and see where we

are at. If, unfortunately, it doesn't work we just go on.

DR. GOLDSTEIN: Sponsor?

DR. CUNNIFF: Tim Cunniff, from Ovation Pharmaceuticals. Dr. Kieburtz, that is a very good point. I think what we are trying to do in that situation through the REMS is that people who do not respond to Sabril, they get removed early on, and we will enforce that. And, the vast majority of data is that the PBFD occurs long-term out from the clinical studies, from the literature, from our postmarketing safety database, through our outliers where it is at two months, but we think, for the vast majority of patients, we can protect them with that enforced discontinuation if there is no clinical benefit in reducing spasm cessation.

DR. GOLDSTEIN: Dr. Kieburtz?

DR. KIEBURTZ: I think that is in general true but I don't think that that is a preventive maneuver that will keep children from having visual loss who have no clinical benefit. I think you are right, it will probably prevent in the vast majority. I think that would need to be part of the disclosure or part of the labeling.

DR. GOLDSTEIN: Dr. Gorman?

DR. GORMAN: I think that I would agree with the general statement so far and add that the risk appears to be appropriate with the benefit, in the sense of if you benefit from this you will continue to put yourself at increased risk for visual loss. I think the plan, as a neurologist, that the company or the sponsor both have is that if it is not efficacious they will be taken off of it fairly rapidly. While there is the risk, the data that we have so far seems to indicate that this is a cumulative risk and we would be mitigating that as much as we can by shortening the course of therapy in the initial non-responders.

DR. GOLDSTEIN: Dr. Kramer?

DR. KRAMER: I would just like to say that at this point I think Dr. Kieburtz' comments indicate to me that this is why the risk communication part of this is crucial because the worst thing in the world would be to say, you know, we are going to meet after this trial to see if it works and we are going to assess, you know, the risk and benefit as if it is known that if you are doing okay at this point in time there won't be any further decline.

I mean, as I was reading the whole packet, you can

imagine families misunderstanding that just because you are having a conversation that you are fine now, that means you are going to continue to be fine. So, I think people writing these things need to be very careful to make sure that people understand and are making the decision to accept the risk.

DR. GOLDSTEIN: As we discussed yesterday, at least the peripheral visual field defects even in adults where you think you can do reliable visual field testing, there were issues and we discussed those in great detail. Today we have the additional problem about the reliability of any assessment in children this young with other disease processes. The risk mitigation and education package is very, very important. There may need to be different language for children being treated for infantile spasms than the risk program that was discussed for adults, but we will leave that to the FDA.

Let me turn to Dr. Katz and Dr. Temple for a second. You have (a) through (g) here, sub-questions, and what I have tried to do here, I have tried to summarize all of those by the general statement that I made that was then also summarized by Dr. Kieburtz in slightly different

language but saying the same sense. Is there anything specific here that you would like us to address in more detail?

DR. KATZ: Well, I think we are really primarily interested in whether or not you think that there is a reliable and practical monitoring paradigm that will catch this early. I think I understand what you said and what Karl said. So, I would just sort of like to get the sense of the group on whether or not they agree with you.

DR. GOLDSTEIN: Let me ask the pediatric ophthalmologists, do you think that there is a reliable, sensitive way, based on clinical exam, that this could be caught early in infants with these types of diseases?

DR. REPKA: Michael Repka. There is no way to reliably predict or detect an early lesion using any of the tests we have clinically available right now.

DR. GOLDSTEIN: Dr. West?

DR. WEST: Connie West. I concur.

DR. GOLDSTEIN: So, I think what we are saying is that visual deficits very well may occur. They very well could be severe before they are detected. They very well could be irreversible, and parents and families need to know

about that possibility. And, even though they may have visual testing, that may not provide any protection against that as a possibility. Dr. Kieburtz?

DR. KIEBURTZ: Maybe I am straying off the question, but this goes to the point of when can you early estimate an assessment of whether there is a response, and how do you indicate that? So, obviously, in some of the studies those responses were detected in two to four weeks. Is it reasonable to start having the conversation about whether it is a therapeutic failure that early and no later than three months? Because I am sure the reliability of the failure is more consistent the longer you have gone but, still, that increases the risk of the exposure the longer you go.

We just discussed that. What type of framing can we put around the period of time? When is the earliest that it is reasonable to start assessing for therapeutic therapy and when is the latest? Because I think that will additionally mitigate the risk.

DR. GOLDSTEIN: We are going to have I think a more specific discussion about question 3 from the FDA that actually is asking us to discuss that in particular. So, I

think we can get to that a little bit later.

I don't know that we need to haveB-I am sorry, some additional questions? Dr. Mizrahi?

DR. MIZRAHI: Just one last issue about risk, and this is something that perhaps ophthalmology colleagues can address, and that is that it seems like we are assuming that the risk will be the same for visual impairment in these young kids as opposed to the adults. If we factor in the developmental issue are we suggesting that the risk would be the same, or are we cautioning that it could be greater or less since we really don't know?

So, as we sort of describe this risk I think it is important to say that what we are basing the data on rather than the hard facts about what has been happening in the younger kids. But maybe I am overstating the developmental issue and perhaps the ophthalmologists can help us with that.

DR. KIEBURTZ: I don't think we have any basis to make a decision on that.

DR. GOLDSTEIN: Dr. Sleath?

DR. SLEATH: I just had a question about who would be seeing these children, especially in rural areas. Are

there enough pediatric ophthalmologists and what is the danger if non-pediatric ophthalmologistsB-yesterday we talked about optometrists versus ophthalmologists. So, with the kids, I would like the ophthalmologists' view on that. And then, to reemphasize it, there needs to be an educational program for ophthalmologists as well in the REMS.

Then the other question I have for the sponsor is about the visual field simulator because I have heard ophthalmologists argue about how you demonstrate this to families. You have that in there as part of the REMS but it is never really specified how it is going to be used to educate the families.

DR. GORMAN: Well, I may understand this incorrectly but it seems to me that most of the visual screening is really going to be done by the neurologist.

DR. GOLDSTEIN: Let me ask the sponsor to respond.

DR. CUNNIFF: I think with respect to the visual field stimulator, what we are hoping to accomplish there, and obviously we have to work this out with the FDA, these are all materials that have been submitted but not reviewed or approved yetB-you know, in addition to the informed

consent documents written in patient-friendly language, it still may be unclear exactly what the effect may be on your vision. So, we are hoping to, maybe through a simulator, kind of show them, okay, this is what you may lose and, you know, in the worst case this is what you may lose.

Now, we have to make sure that that is giving an accurate story too because these simulators often have flaws and it doesn't really show the real-life situation. So, that would be something we would need to work out with the ophthalmologists at FDA to make sure we are really giving a sense of what peripheral field loss might be.

DR. SLEATH: But I guess part of my question is who actually is going to do that? The prescribing physician? Because I would think you would want to educate them before the point they see the ophthalmologist. Or, is it the specialty pharmacy? That is kind of what I wonder.

DR. CUNNIFF: Correct, so I think it would be available in their initiation kit. So, it would be the initial prescribers, the neurologists or the pediatric neurologists walking through it with them. I think we would also make it available to the patients and the families on the web site too so they could refer back to it in case they

had any questions, just to help inform them in their risk decisions. Dr. Pellock has another point he would like to make.

DR. PELLOCK: I could do this globally and ask the adult neurologists what you would do when a kid with spasms walked in, but I know the answer is call us.

So, the child neurologist is the person who sees these kids. They are sick kids. They have other problems. And, we will not only be the persons who confirm the diagnosis and counsel them about treatment and then begin treatment, but we will be the people who see them often, take their phone calls many times a week frequently, and help monitor the process.

I am sort of repeating myself somewhat but I think it is our concern, the parents' concern, either a change in a physical examination or history or concern, that will prompt then referral to a pediatric ophthalmologist or ERG laboratory or a neuro-ophthalmologist, whoever is available.

One of the findings of the Epilepsy Foundation AES conference a number of years ago, national conference, was that in fact there weren't enough pediatric neurologists. Mothers and fathers with kids with this kind of epilepsy and

others want a child neurologist in their town. Well, there aren't enough of us. So, we share the responsibilities but essentially most of us will be running this as far as, you know, guiding the families through it and making special provisions for those who really do live far away.

DR. GOLDSTEIN: Thank you. Dr. Rizzo?

DR. RIZZO: Thanks. So, we are concerned that we are not going to be able to reliably detect visual loss with the electrophysiologic techniques and, yet, visual loss is detected at some point, and I gather somewhat reliably because we have figures on visual loss.

So, can we identify a cut point where we can actually reliably identify visual loss? Is it moderate? And, can we say that even in cases of moderate loss acuity will remain normal? Are there subsets of patients who can be tested reliably? What are the data in normal infants? Can they be reliably tested with ERG or is it just technique in this age group?

DR. REPKA: Well, the sponsor may want to speak to the ideal situation which Dr. Westall has. I think the reality of this is that you almost have to plan as you roll this into a neurology practice that you have a plan for an

ophthalmic consult and the potential for getting an ERG consult as a way of detecting or confirming the supposition of visual impairment.

I think the reality is you can do an ERG in everybody if you happen to have a general anesthesiologist and you happen to have an electrophysiologist handy. There are way fewer of those than there are pediatric neurologists or pediatric ophthalmologists. So, access is really the problem for that service, as well as the expense which will be another aspect of this.

DR. RIZZO: I want to make sure we don't throw out the baby with the bath water, and what I mean is that at some point even if the ERG isn't helpful for minimal loss, maybe it does become useful at some point so we shouldn't discard the idea of using it even if it is only minimally available in some places.

DR. REPKA: Well, I think that that remains to be seen, what the ERG abnormalities turn out to be in these kids who are actually able to do visual function at an older age. In fact, the long-term visual outcome that we noticed earlier didn't exist in the data. So, that is I think something we need to know, the ERG findings.

The other problem with ERG is its test-retest variability, and that is going to make it hard clinically. We experienced that ourselves a decade ago, what to do with a result when one time it is here and the next time it is at another level.

DR. GOLDSTEIN: And I think in the review that the FDA showed, it showed the issues related to ERGs. Even if it can be done reliably, the noise in the system makes it problematic at best.

DR. RIZZO: But at what stage?

DR. GOLDSTEIN: As I understood it, in treating kids and trying to evaluate kids in this age group.

DR. CUNNIFF: Tim Cunniff, from Ovation. Just to respond, it is a very, very good question. I think our impression is that in a well qualified center that has experience in doing ERG it is reliable, and it is a question of access as well as the expertise to do those types of tests.

I think we could work into the labeling, and Dr. Pellock mentioned it, that when the child neurologist takes care of the patient there are things they do, whether it is a physical exam, whether it is a change in something going

on, that would prompt them to refer their patient to an ERG center or to a neuro-ophthalmologist. I think we can perhaps, through the labeling, through the REMS, educate on those concepts as well. And, I think if there is an issue and it is the reliability of reading, certainly we can have something centrally read by an expert who can interpret it. I think that would be another safeguard.

DR. GOLDSTEIN: Dr. West?

DR. WEST: I don't think that we have any data that correlates ERG amplitudes or implicit times with visual fields in children in a reliable fashion. Thus, you are left with using adult data, which may or may not be accurate, and then I would point you to sponsor slide CDC-8 from yesterday morning which showed ERG b-wave amplitude so that is the amplitude of the electrical response of light-adapted cone responses to the kinetic perimetry mean field radius, which I am hoping is a typo because you don't really have a radius of a field; you have an arc of the field, but anyway.

You can see though that if you had a b-wave amplitude of 50 or 60 you could have no field constriction or massive field constriction. So, what do you do with that

practically? If you had a reduced amplitude in a kid in whom this medication was controlling the seizures very well, what the hell would you do with it? You wouldn't know what to do with it, practically speaking.

DR. WESTALL: I would like to answer the question. My name is Carol Westall, Toronto Hospital for Sick Children. Some very, very good points are being brought up, and you are absolutely correct. in the infants I cannot do Humphrey visual field as well as ERG. What I can do is look at what I consider a real drop in the ERG and I know that there is a toxicity going on in the retina.

We have had comments about test-retest reliability as well as developmental data in these children. There are published reports. Westall et al. published the development of the infant ERG in '99 and Fulton and Westall also published some normal data on development.

On test-retest reliability in adult studies the ERG is used to monitor retinitis pigmentosa. There is a test-retest variability which, in the adult population, is about between 42 and 50 percent. That is a drop in 42 to 50 percent. In the infant population I have studied, a drop in 50 is the variability. So, basically a drop greater than

that would be significant.

So, in the data that the FDA has described I am very impressed with their picking out the small points, but I would also like you to notice the lack of the developmental curve in that data as to the growth of the ERG.

DR. WEST: Exactly. I mean, I have carefully read your articles in Documenta Ophthalmologica II because I wanted to come to this prepared. I very much respect the work that you do and I would love it if you would come to Cincinnati Children's and work there instead.

But the other thing we haven't talked about as a group is that the ERG wave forms evolve with age and mature, and are not the same at one month as they are at four months, as they are at seven months. So, then you confound it even further by trying to figure out what sort of trajectory that child's ERG is developing on. So, to all practical purposes almost no medical center, even a tertiary care medical center, has the ability to do that type of testing. I think it is very specialized work that Carol has done.

DR. GOLDSTEIN: Dr. Katz?

DR. KATZ: Yes, I think it is clear and we sort of got the sense of the group that you don't think there is a reliable, practical way in which we can test these kids and pick up a lesion early. Fair enough.

Remember, in adults yesterday we said we are going to require periodic ophthalmologic monitoring. So, given that we don't think there is a good way to pick it up in kids, as distinct from adults, should we in the REMS require periodic ophthalmologic examination anyway? And, if we should, how often should we do it? Or, should we just write in labeling use your best judgment as to whether or not you think your particular patient needs to be seen by a specialist?

DR. GOLDSTEIN: And one way to deal with it is by saying in the labeling that visual deficits are likely to occur. Given the range we have seen, they may or may not but are likely to occur. They could be severe and they may be irreversible when first detected. The neurologists that are following the children will be doing visual assessments every time they see them and referring them to an ophthalmologist as needed.

From what I heard from our ophthalmology

colleagues, they could be looking at these kids and not be able to detect anything reliably either. Correct me if I am wrong. Is that what you were saying?

DR. CUNNIFF: I think that is fairly accurate.

DR. GOLDSTEIN: Dr. Kramer?

DR. KRAMER: Actually, before Dr. Katz said what he was going to say is when I raised my hand. I just want to make sure that we are clear that the REMS program that was presented yesterday may not be the same as what we are talking about today. I was really getting at the question of whether we were really-Bit didn't make sense to me that on the one hand we said the only way to do it and now we are talking about requiring them to see an ophthalmologist.

DR. GOLDSTEIN: Dr. Lu?

DR. LU: I think the FDA raised in the morning that whatever the finding is, I mean, there is a need and there is a way to verify the gold standard case and I haven't heard anything about that.

DR. GOLDSTEIN: Dr. Kieburtz?

DR. REPKA: Dr. Pellock said something earlier that really resonated with me. I just wondered if Dr. Dure and others couldB-I mean if I paraphrase him, I don't want to

quote him incorrectly, but a detailed history about issues of visual function by a pediatric neurologist might be as good as any other test. I just wonder what the ophthalmologists and pediatric neurologists think about that. If I quoted you wrong, I am sorry. Does that sound right? Because, I mean, mandating ophthalmologic monitoring might be making ourselves feel like we are doing something more effective than we are rather than saying a targeted history and physical. I just wonder what you guys think.

DR. GOLDSTEIN: Dr. Dure?

DR. DURE: I won't speak for everybody. We may have a variety of opinions, but most of what pediatric ophthalmologists do is observe. So, we take good history; we observe children. I think on the whole what Dr. Pellock says is correct.

But one thing that I would say is that doesn't mean that we probably shouldn't or at least push for some sort of prospective observation of visual loss at some point. It does sound to be reasonable, you know, to check them. I would be satisfied with a neurologist screening them as long as we are very honest that it is not going to be all that sensitive necessarily.

DR. GOLDSTEIN: Very good. Dr. Gorman?

DR. GORMAN: I could see a parallel between this situation and discharge from the intensive care nursery where sometime in the future there is a prescribed visit to the ophthalmologist. We don't think we can pick it up early but we do think we can then characterize the risk for patients who choose this therapy later.

DR. GOLDSTEIN: Dr. Weinstein?

DR. WEINSTEIN: Listening to some of the parents that talked, I think it supported my sense that what they see early on is visual inattentiveness. Does that mean that if we have a child whom we are unable to really assess because they are inattentive, do they all need to go to the ophthalmologist? And, I guess the question then isB-I have no idea what the percentage is that are like that, but are ophthalmologists going to do any better, and if they are inattentive how are we going to pick up a change?

DR. GOLDSTEIN: Again, they can respond but my sense was that they can't say that they can reliably pick up anything better than the pediatric neurologist evaluating the child might. But let them answer.

DR. REPKA: You could have taken the words out of

my mouth. In fact, you took the words out of my mouth. In fact, I would argue that it might be worse or better depending on the day. These are very difficult children, even with a long history and observation, to decide whether in fact there is a field defect.

DR. GOLDSTEIN: Just one other issue, and that was question 5, and I think we have beaten peripheral visual loss into the ground. What about central visual loss? Have we seen any specific data to answer that question one way or the other?

My view, just to summarize, is that we haven't seen data, just as we haven't for peripheral visual loss. Does anyone have any comments differently? Dr. Katz, let me leave it to you. Is there any specific other letter question here that you want us to address for you that we haven't? I don't think we need to do formal votes on these things. I think you get a pretty good sense of what the committee thinks.

DR. KATZ: We have a very good sense of the issues that you have discussed. The one issue is basically question 3, which goes back to efficacy. Again, there is a view that for example with ACTH you treat for a couple of

weeks and then, in those kids that respond, they are done. You might have to treat them again later on for a two-week course.

But the question is should we require the sponsor of vigabatrin to do a study in which they look at varying durations of treatment and see the results according to duration? Maybe you only have to treat for a month and these kids are just as good as if you treated them for six months. I don't think we have that data. The question is, is that the kind of thing, if it were to be approved, we should require?

DR. GOLDSTEIN: Let's come to that, if we could, in a bit because I would like to go through the toxicity. Is there anything specific with the visual things that is question 4 with its various sub-letters in question 5?

Let's switch to the other piece of the toxicity puzzle. Those I think are items 10 and 11. We heard data about the pathology in animals and issues related to that. We had some potential suggestions from the FDA as to how that could be addressed in the future. But also there was the question on the MRI, question 10, and specifically does the committee believe that intramyelinic edema seen in

animals has any clinical consequences in pediatric patients?

We saw the data in adults yesterday. The data in children is somewhat different. The MRI appearance is different and the pathology may be somewhat different. Are there data to address this? Yes or no? Let me just open this for discussion. Dr. Jensen?

DR. JENSEN: I thought we also made the statement that we didn't think that the intramyelinic edema was necessarily at all related to what the MRI findings were, and that there were gray matter changes seen in the developing brain and they weren't the characteristic white matter changes that have been described in the studies, in some of the rodent studies. So, I thought the discussion meant that these were two potentially very separate entities and the link had not been made.

DR. GOLDSTEIN: That was my sense also. It says intramyelinic edema but I think we are talking about the MRI changes. So, are there changes on diffusion-weighted imaging in the deep gray matter structures that wouldn't necessarily correlate with that? Pathologically we heard about the changes and it doesn't appear to be the same types, or may not be those same types of issues. There is a

question pathologically about whether there is apoptotic cell death that couldn't be addressed because the stains weren't done. Dr. Katz?

DR. KATZ: Yes, right, I think there are potentially two things going on. This question was just asking whether or not we think the intramyelinic edema, which we have been dealing with for 15 years, has anything to do with pediatric patients.

The next series of questions deals with this presumed different lesion, and is that related to the MRI, and does that have any clinical consequence. So, this was really just sort of the first order question. The old lesion, let's put it that way, does that have anything to do with pediatrics?

DR. GOLDSTEIN: Do the people on the committee have any comments? My view is that we have no data. Again, looking around the room, does anybody disagree with that? Cool.

The other lesion, my summary would be the same, that there is this potential pathologic lesion. We have a different pattern of MRI changes and the clinical significance, if any, of that remains unknown. Do people

agree with that? Outstanding.

So, given those two things, and we have talked about the two major types of pathology, the visual issue and the MRI and potential pathologic changes, let's look at question 12. I think that is the next logical one to hit. That is, should additional safety data be obtained prior to approval if we recommend approval for this indication, additional safety data, the safety study that should be done?

Now, remember, we also have this MEMs program afterwards that would presumably be monitoring children and there are various components of that that could be discussed. But prior to approval, is it the sense of the committee that additional studies need to be done?

Would you guys like a final vote or can I do this by consensus also?

DR. KATZ: No.

DR. GOLDSTEIN: So, by consensus then, do additional safety studies need to be done? Yes? No? I think you have a sense there.

Then, the next sub-question, again trying to follow this in some logical order, is question 9. Can you

put that one up?

[Slide]

Given the off-label therapy, again provided that we feel that the drug should be approved, do the safety concerns that we talked about, the potential visual loss, couched in all the terms and all the education that we said would need to be done, as well as these potential MRI changes, as well as potential pathology, and given the alternative off-label therapy, do these safety concerns preclude marketing even if efficacy is demonstrated? Comments? Nobody has any comments? Oh, there we go.

DR. JUNG: No, just a question. Could you clarify what you mean by preclude marketing? Is it advertising?

DR. KATZ: Approval. We mean approval.

DR. JUNG: Just approval?

DR. KATZ: Right.

DR. GOLDSTEIN: Dr. Jung is asking for me to clarify it again. What they mean by marketing here, they mean approval. I guess they used the wrong word.

DR. KATZ: We think of it as the right word. We use them interchangeably in this context.

DR. GOLDSTEIN: You are killing me! Strike

marketing; put in approval. Given the alternative off-label therapy, do the safety concerns we talked about--which are not to be minimized, they are potentially significant, do those safety concerns preclude approval even if efficacy has been demonstrated for this drug? Comments?

Okay, let's try it. Do the safety concerns preclude approval even if efficacy has been demonstrated? Yes? No? Abstain? Outstanding. You have our consensus.

Now I think what we can do is go on to questions 6, 7 and 8 together. Why don't we try those, 6, 7 and 8? Can the committee envision any combination of patient populations and conditions of use that would support approval? I guess that is almost a semi-moot point since that is what we have been talking about.

Unless someone has an objection, let's go on to 7. If the answer is yes to question 6, what is the appropriate population? This I think we do need to have a little bit of discussion about. Is it all patients with infantile spasms, only age-specific subsets, etiologic subsets such as tuberous sclerosis, or patients who have failed other treatments?

Let's try to have a little bit of discussion about

that for the FDA. Dr. Mizrahi?

DR. MIZRAHI: You know, I have been struck with the data and also discussions about an improvement in those children with spasms based upon tuberous sclerosis. But I also think that there is enough information to not restrict it to that category of etiology.

I still think we don't know enough about the various etiologic factors and cryptogenic and symptomatic or idiopathic patients, those three categories, that we should restrict it to one very specific etiologic factor. So, I would be in favor of it for all-comers with infantile spasms, rather than a focused group.

DR. GOLDSTEIN: Thanks. Can you put up CEEI-9? Sponsor, if you all have any other data specifically relevant to this that you would like to refresh everybody's memory about, I would appreciate it.

DR. SAGAR: I am Steve Sagar, from Ovation. The data concerning the efficacy across etiologies is the 1A data you see here. There is the data from UKISS, which I spoke of earlier, in which tuberous sclerosis patients were specifically excluded from that study and had a combination of symptomatic and cryptogenic patients in which vigabatrin

had about a 54 percent, as I recall, spasm-free rate after 14 days of therapy in both of those populations. So, that is the main data that we have for the issue of efficacy across etiologies that has been examined best.

DR. GOLDSTEIN: So, the sense that I have had so far is that I haven't heard anything saying that there is one specific subgroup for which we have data suggesting that it would benefit and other subgroups might not for infantile spasms. Dr. Chugani?

DR. CHUGANI: Well, I just wanted to point out that there are certain patients with infantile spasms where we would be careful, particularly careful. For instance, if a patient already has a hemifield cut for a different reason, like a patient with Sturge-Weber syndrome for instance, and they only have one field left, and if you then get a constriction from vigabatrin on that field you are going to be left with tunnel vision basically.

But I am not really advocating a contraindication. I think it should be left to the practitioner. But I think it should be cautioned. I am just interested to see what Dr. Shields or Dr. Pellock have to say about that.

DR. SHIELDS: Don Shields. I completely agree. I

think these are things that go on in the discussion with the family about the options that are available to them, and the families help us decide which one we are going to use. I mean, I have presented the same information and one family says I think we will do the ACTH and another family says I think I will do the vigabatrin.

So, I think these are parts of the discussions and I would really not want to see some kind of restriction on this group or that group, or leave that group out. There may be patients with Sturge-Weber that fail a couple of drugs and you want to go back to that because that is the best chance they have. So, it is all going to matter in case situations.

DR. GOLDSTEIN: Thank you. Dr. Dure?

DR. DURE: Yes, I would just echo those comments. I don’t think that there is justification to parcel out these patients. But I would say this, that for the registry every effort should be made to make certain that we know what patients are being captured, what the etiology is or if the etiology is known.

DR. GOLDSTEIN: Dr. Kieburtz?

DR. KIEBURTZ: I think, given the risk, it is

important to think about the data we looked at. It sounds like we are edging towards saying this might be approved, hence my question earlier in the day. I think the vast majority of the data happens from individuals who are under 24 months of age when they are enrolled in the trials, and I think we should probably be careful about maybe the right subset, under 24 months of age, or at least ascribing that the data derive from that population.

I think the other is about this issue of preexisting visual impairment that makes a reasonable caution also about initiation of treatment.

DR. GOLDSTEIN: Does anybody think that additional efficacy studies should be done in specific subsets of patients, or are we okay with data that is available now, you know, given what we have in hand, the sub (b) question here? I don't see any overwhelming opinion about that.

Question 8, which also was predetermined by 6, was should a risk evaluation and mitigation strategy be used? I think the overwhelming opinion here was yes with additional details, maybe changing it specifically for better education about the child population as compared to the general population. Dr. Kramer?

DR. KRAMER: I think we should specify what we think the crucial components of that would be for this population as opposed to what we talked about yesterday, as I said earlier. And, it seems to me from everything that has been said that the things that are crucial is absolutely clear communication so that the families know what they can reasonably expect, and not mincing words about it, that visual changes are likely to happen; that they are probably irreversible; they do happen. They have to be prepared to accept that, and that they can't necessarily be detected early enough to prevent it.

So, I think that is crucial. I think that the other thing that is crucial, besides that communication and understanding of the families, is the registry component. And, I think we said earlier that we don't think the ophthalmologic monitoring should be required.

DR. GOLDSTEIN: Dr. Gardner?

DR. GARDNER: We are putting a lot of emphasis on this REMS program, and I would like to ask Dr. Cunniff to talk to us a bit. Yesterday you, and perhaps others maybe in your group, said several times Ovation is a small company but dot, dot, dot, and I look at this REMS program,

specifically a registry attestation of physicians, data collection through specialty pharmacies, and so on, and I see either a huge or substantial infrastructure in-house or an expensive contract externally in order to mount and manage this, especially over a long period of time, and we are asking, between yesterday and today, for data collection and reporting over a long period of time.

We have had other experience in risk management registries and they are a lot to do. Would you talk to us just a bit about your plan for implementation that will give us some confidence that what we are banking on here can be done?

DR. CUNNIFF: Sure. I would say, first of all, that our business at Ovation is that we specialize in these very rare conditions with unmet medical needs. So, we are very efficient in what we do. We have a very dedicated staff so it allows us to do a lot with somewhat limited resources. But I think as we are growing we are one of the leading specialty pharmacy companies in the U.S. right now. So, you know, I wouldn't call us a small company anymore. I would say we are a medium and growing company.

We definitely have the resources to support these

programs. We just launched a drug for Huntington's chorea that also has a REMS and we have implemented that. We have launched that drug and that is ongoing. We have a 22-patient regulatory group at Ovation and we have a 23- or 24-person patient organization.

So, I think if you count up the regulatory and patient safety folks we are about a third of the company, and that is because of the investment into these programs. Obviously, we have support for advocacy groups and all the support from the community, whether it is the ophthalmologists, neurologists, the child neurologists. And when we do have data safety monitoring committees a lot of individuals volunteer their time or they take a very limited salary to keep the cost down.

We do use outside vendors. I think for this particular program for the specialty pharmacy, the central hub that is contracted out, those contracts are all signed already to go on that. Some of the knowledge, attitude and behavior surveys, that is also using a specialty group and epidemiologists that will help us design the surveys to figure out if the REMS is working. We say we are going to be educating patients and physicians. We have committed to

periodic time points to send in reports to the FDA to make sure that the REMS are working.

We have looked at other REMS. Some of those have had to require revisions as you collect that data, and we are very committed to do that. And, we have an independent monitoring board, helping us in making those determinations as well.

DR. GARDNER: Let me ask about something specific that relates to today's topic. One of the things that we hear from parents is about time, and the time not only that it took to identify the problem but also waiting for drug to be delivered from Canada, or wherever else they find it.

We found in the registry or the restrictive risk management program for Accutane and generics that a huge issue came up initially because with pharmacies needing to call in to verify that the prescriber was legit that the patient had been consented or agreed, and so on, and confirmation of these things. Sometimes there were huge delays. They were mostly a frustration for the pharmacist to hang on the phone until he got it sorted out.

But I guess my caution to you would be, given that time is an issue here and a frustration, I would ask you to

be sure that you begin your program, if you haven't already in some other form, with that in mind so that, once you push the button and say we are going on this, you can deliver your system and your drug to the people who are calling for it at the time they need it right away.

DR. CUNNIFF: An excellent point. I think we have learned from some of the experience you are talking about too and we do not want to fall into that same trap. So, we will be ready.

DR. GARDNER: I am sorry, one other thing. Will the specialty pharmacies be mailing or shipping--

DR. CUNNIFF: Correct. There would be a FedEx system where they would receive it within 24 hours and we would probably also have starter kits at the tertiary medical centers because we understand if a parent and a patient have to wait a day, that will probably be too long.

DR. GOLDSTEIN: As a corollary to that, I think you said that children that need to be seen by a pediatric neurologist almost on an emergency basis to begin treatment as soon as possible, there is going to need to be education not only of the public but also of the medical community about this. So, the general pediatricians would need to

know and neonatologists would need to know that this is available, and the systems have to be put into place to be able to provide the therapy as quickly as possible.

DR. CUNNIFF: And we know our community very well. We have very good relationships with them. It is a small community to cover but that is where we specialize and that is where we focus.

DR. GOLDSTEIN: So, in terms of 8(a), I think we have talked about this. This was already in their program in terms of the restrictive conditions, practitioners, etc. Any other specific comments about that? Yes, Dr. Crawford is next.

DR. CRAWFORD: Thank you, Mr. Chairman. For the sponsor again I have one comment and a question. The question is very related to what Dr. Gardner has said. My comment would be something that Dr. Kramer had mentioned, as well as the chair, that I don't think that the same REMS should apply for this indication and population as you presented last time.

Even some things that have already been stated, as well as when I look at patient caregiver education, the majority, if not all of these patients, either infants,

toddlers or minors, I don't think the patient-physician agreement is the right term. It should be the caregiver for example.

My question, to follow-up a little bit on what Dr. Gardner stated, I am still a little shaky about the true population of patients and my question to the sponsor is about your best estimate of the demand if this drug were approved for this indication. Because we heard you say perhaps 2,500 total.

If I just listened to the physician specialists in this room, both from the sponsor and around this table and from the public hearing, that is almost more than 2,500 patients. Dr. Kossoff in the open public hearing, he believed that the estimate was far larger, which it could be and still meet the criteria for a rare disorder. So, would you please address that?

DR. CUNNIFF: I think I will take the first part and I will defer to our pediatric epileptologists. I think the incidence is about 2,500 new cases a year. I think the prevalence, I want to say, is about 8,500. I have seen that somewhere. Then I will have Dr. Pellock address maybe how that would break out between the various treatments.

DR. PELLOCK: Dr. Pellock. I totally agree with that estimate. Once an infantile spasms patient who does not completely respond, or even if they blink an eye, the child neurologist hears about them again. So, it is like we think we have ten times the numbers because the fact is we see that particular person so frequently. Right, guys? I mean it is really what happens.

But the true incidence, and there are a couple of really good epidemiologic studies, one in the State of Connecticut and one in Atlanta, and general population studies done through CDC that relatively confirm this incidence number.

That I think is the challenge of, as you pointed out, educating a person, a general pediatrician who may not have seen a patient like this since they were in training. We need to continuously remind them and reeducate them about appropriate referrals. So, you are absolutely right.

DR. GOLDSTEIN: Dr. Katz, Dr. Temple, do you have enough information about the risk? Okay, excellent. Now, the second to last question is the issue about duration of treatment. Yes, Dr. Kieburtz?

DR. KIEBURTZ: I just want to get in on 8(c).

DR. GOLDSTEIN: Sure.

DR. KIEBURTZ: And maybe this goes to the question, but I just wonder if continued access to the drug shouldn't be linked to monitoring for therapeutic benefit. I don't think we have said anything about that specifically.

DR. GOLDSTEIN: I think that is what we are going to do in question 3 now.

DR. KIEBURTZ: All right. If that is so, I think there might be an implication for 7(b), which is about subsets, I know, but I just wonder if maybe we can discuss it under 3, are there designs that might be implicit on the sponsor about getting at this issue in a more prospective way.

DR. GOLDSTEIN: That is where we are now so let's start talking about it some. This is the issue under question 3. I guess the core of the question is whether additional trials should be done looking at duration of therapy, and what advice we might give in terms of frequency of monitoring and duration of therapy since, given what we have seen, I guess there are two models. One potential is a short-term treatment model and the second is a longer-term treatment model.

One thing that I was just playing with to put out there also, again in terms of advice or labeling, if you will, was that treatment with drug should be for as short a period as possible to limit exposure, given the goal of trying to prevent infantile spasms, given the likely increase in toxicity with treatment over time.

I think we have heard from a couple of pediatric neurologists that have used the drug that that is basically what they do, that after a period of timeB-one year is what I heardB-they may try reducing the drug and if they recur then you go back for another period. That is what Dr. Shields had mentioned. But, again, this is open to discussion now. Dr. Chugani?

DR. CHUGANI: I think Dr. Shields also mentioned that the exception is tuberous sclerosis where you would be less likely to get rid of the medication too quickly. You would hang onto it because those kids do so well with it. So, there is a chronicity in that population with the use of this drug, and I would be interested to see whether the other child neurologists agree with that.

DR. GOLDSTEIN: Comments? Dr. Katz?

DR. KATZ: What we are trying to get at here with

this question is to see whether or not we should require the sponsor to require them to generate data to look at how long is long enough. In other words, maybe if you treat for a month with vigabatrin that is as good as if you treat for six months.

So, in this case that information would at least be interesting more than the typical case because here we think there is a toxicity that is related to cumulative exposure and we can't monitor for it. So, here in particular there might be great interest in trying to figure out what is the minimum duration of treatment that will get the job done.

DR. CHUGANI: For all patients?

DR. KATZ: Well, yes, I am thinking of it in terms of all patients for whom you might approve this. You know, the answer to that question might actually differ depending on what the etiology is but, you know, that is a second order question. The idea is should we get data that establishes the minimum duration of treatment that will do the job.

DR. GOLDSTEIN: And if so, what model would that fall under? Dr. Temple, you also wanted to make a comment?

DR. TEMPLE: Yes, one possible approach-Bit doesn't quite do what Rusty was hoping for to find one whether one month, two months or four months, is to, perhaps working backwards, start doing randomized withdrawal studies after a certain period of time that everybody considers to be okay. Like, if most people think you need to go at least six months you keep some people continued at six months and withdraw the others. Of course, if anything came back you would immediately resume therapy.

This is going to be a sensitive point. We already know people are going to be somewhat reluctant to take the drug away. In this case you would have to, I think, have to start with what most people think is long enough and prove that that is true. I mean, we don't even really know that. So, maybe starting out with people who have been on it for a year and then moving back if that seems to not do anything to people who have been on it for a shorter period of time. I mean, we would have to work out the details. But that is sort of what we do with maintenance therapies now.

DR. GOLDSTEIN: I guess the point is that the studies that we have seen have been relatively short term. Some of the patients were maintained on it longer term

afterwards, but in terms of the design you are talking about, we haven't seen any data like that. Dr. Snodgrass?

DR. SNODGRASS: Yes, I agree theoretically. Like, a randomized withdrawal, that probably could well be done and might be strongly considered.

The only other point I want to bring into this and, again this may be theoretical but I think there probably are other examples where this may have occurred maybe in other disease processes, but if you withdraw and then there is a recurrence of seizure and you start them back again, it is sort of like bacterial resistance. Right? Now they are not responding as well to therapy compared to if they had been left on it. So, the question is how that might be addressed.

DR. TEMPLE: Of course, you will get to compare the people who were continued on and you can keep following them for three months more, six months more so you will get to see what happens to the people who were withdrawn. Maybe nothing happens but if they do get a disadvantage you can see whether adding the drug back then puts them back where the other group was.

Now, you know, there are going to be

discontinuations and all this. It is not going to be perfect, but you do get a shot at doing that. And, of course, the argument for it is that there is a consequence to keeping giving this if you don't need it.

DR. GOLDSTEIN: Dr. Kramer?

DR. KRAMER: Yes, I actually think this is the one situation where you could get objective data. I think it should be not a prior to approval question but I think the idea of a randomized withdrawal study post-approval in the situation where you already have equipoise, where you are really not sure that continued treatment is necessary, whatever that cut point according to the neurologist assessment would be. So, I would strongly support that design.

DR. GOLDSTEIN: Dr. van Belle?

DR. VAN BELLE: It strikes me that trying to answer these kinds of causal questions by means of a passive registry is fraught with danger. If you want to go that way, you should really go to a randomized trial or even have some prespecified plan for the analysis of the data as it comes in, including quality control and so on. It is unlikely that a registry by itself is going to answer this

kind of question.

DR. GOLDSTEIN: Dr. Weinstein?

DR. WEINSTEIN: It strikes me that the company must have data from its studies that talked about recurrence risk, and I suspect they also have data as to what the next drug was and whether they went back on.

I hear what Dr. Snodgrass says. Before you putt something, and you are talking about it being a devastating disease, I think you want to know that you haven't made them worse before you start withdrawing them.

DR. GOLDSTEIN: Dr. Nelson?

DR. NELSON: Yes, I was actually going to comment similar to what Dr. van Belle said, but I do fear that it might be hard to enroll patients in a withdrawal study. They may not be interested in having the drug withdrawn prematurely based on whatever standard they presume they should be taken the drug for, whatever period of time.

I am not negative I guess about the database study as long as it is, you know, prespecified because there are going to be people who fall off of therapy for various reasons. I think if we monitor those people perhaps and try to make some sense of that data it will at least provide a

nidus of information by which you could maybe approach people to do a randomized study.

DR. GOLDSTEIN: Dr. Chugani?

DR. CHUGANI: Yes, in the old days I used to treat these kids for two or three years, and the rationale was that most kids, when they are about two and a half, three, they have outgrown the window for infantile spasms. And, that is what I used to tell the families. But then we the Europeans changing it to six months or so before they withdrew, I sort of adopted that practice as well.

And, I have met with resistance because these families have been through hell and finally they found this medication that works, and then six months later I am telling them I am taking you off of it and they don't want it. They don't want it. Some do go along with it but others don't.

But it is an area where I think we really need data because I don't know whether it is six months, four months, three months.

DR. GOLDSTEIN: Again, you know, I think it is interesting because this obviously would be done under a research protocol and under informed consent, but the point

here is I guess there is equipoise that we believe there is increased visual toxicity over time. We don't know when it becomes severe. We don't know when it becomes irreversible in any individual, and we don't know for sure what the benefits or risks are of stopping at some point. Exactly what that point is I guess is debatable and what subpopulation. But that is one way of getting at that data. Dr. Lu?

DR. LU: Yes, I just want to echo Dr. van Belle that the prospective, randomized design in this case will answer the question. I mean, a registry, no matter how good it is, always, you know, cannot really answer the question we are interested in.

DR. GOLDSTEIN: Dr. Twyman?

DR. TWYMAN: Just another consideration maybe is instead of completely withdrawing the drug is to drop it to the low dose, and maybe in maintenance you may not need such a high dose and that would offer some level of protection perhaps before you completely withdraw the drug.

DR. GOLDSTEIN: Dr. Gorman?

DR. GORMAN: As long as we are suggesting designs, let me suggest an alternative design which is to

breakthrough seizure then randomize the three groups, increased dosing, same dosing or no dosing. That way I think you would be in a better place in terms of equipoise.

DR. TEMPLE: Say that again. You keep them on therapy and then?

DR. GORMAN: You reach the point where people think it is effective. The Europeans have chosen six months. If they break through after six months with seizures a third gets increased dosing, a third stays on their dosing and a third comes off their dosing.

DR. GOLDSTEIN: A different clinical question but related.

DR. TEMPLE: But there wouldn't be anybody automatically taken off like the Europeans do?

DR. GORMAN: I would wait for clinical practice to determine that particular situation. But to answer your question about withdrawal, I think that if a patient is doing well on a medication that is reversing a devastating disease, taking them off that medicine might be difficult.

DR. TEMPLE: But you said different things. Judy thought there was equipoise on the question of whether you continue after one year or not. If there is and if a lot of

people stop, then presumably you can do the study.

DR. GORMAN: I am not saying you couldn't do the study by going through an IRB. I am saying you may have difficulty doing a study from a recruitment point of view.

DR. GOLDSTEIN: I guess that is something that can be worked out. Dr. Kramer?

DR. KRAMER: I was just going to say that, you know, the whole issue about being able to recruit is coming up with something where there truly is equipoise when you know there is increased risk and, you know, two years. But there is some point in time where you really don't know that you are adding anything. Should people stay on it five years? At some point people are going to get nervous that the risk is counterbalancing and you don't know if they continue to need it. So, I am just saying for the experts to come up with that point. Then you will be able to enroll because the patients can be convinced. You know, six months may be way too short for them to be comfortable.

DR. GOLDSTEIN: I guess the issue is that we don't know that prolonged treatment is a benefit. We do think that prolonged treatment increases visual risk and where is that point that one would withdraw in that risk/benefit? We

have no data for that.

That is one design for dealing with that. Dr. Gorman's suggestion is for a somewhat different population. That is the 20 percent or so that break through and have recurrent seizures, you could then randomize them in that way, increase, decrease, whatever. Different populations. Dr. Temple?

DR. TEMPLE: If someone has a breakthrough seizure is anybody going to let you leave them untreated? Would that be right? That doesn't seem like the group that people would be happy to have you do the study in. It is the ones who are doing fine where you might decide I want to find out whether I still need it to see whether it is worth messing up their eyes.

DR. GORMAN: I would be delighted to have you come and sit as an expert at my next IRB meeting. Thank you.

DR. GOLDSTEIN: Dr. van Belle?

DR. VAN BELLE: Let me get back to the registry. One of the issues would be if you have a patient who stays on for the first three months and then drops out. That is the person in whom you really want to know what is going on at age two. So, unless you have an active cohort-like study

you are not going to find that information. So, there must be some planning for collecting this kind of information to get valid inferences.

DR. CUNNIFF: Tin Cunniff, from Ovation. An excellent point. I think we heard yesterday from the committee that even when a patient goes off a drug there is still a desire to get some follow-up visual field testing. So, we will collect that as well.

I think with respect to the second point about getting some prospective data in that manner, we have already committed as part of the NDA submission that we would do a phase 4 prospective, longitudinal study, a very long-term study looking at neural development and cognition, and also doing serial MRI monitoring to try to see if this MRI issue has any clinical correlation. So, that trial is already on the books and that could be a mechanism to get that information.

DR. GOLDSTEIN: Dr. Kieburtz?

DR. KIEBURTZ: I might have missed it, we talked about what the definition of responding is. Is there some minimal improvement that must be documented in order to continue with treatment so that at one-month or three-month

time point when the decision is made is there enough therapeutic benefit to continue, do we want to give some guidance on that?

I mean, obviously the most dramatic response is cessation and absence of hypsarrhythmia, and we heard earlier you might have a 95 percent reduction in seizures but that still puts you at long-term developmental risk. But still, would we consider that enough therapeutic benefit to warrant continuing the drug? Because I think practitioners might benefit from some guidance about that issue. What amount of benefit is sufficient to carry the burden of the risk of continued exposure?

DR. GOLDSTEIN: And when should that decision be made? Dr. Shields?

DR. SHIELD: I think this comes right back to clinical practice again. Somebody who has a five percent response, it is almost not measurable at five percent. You are going to say that person is really a failure and you are going to take that person all the way off. Somebody who has a 75 percent response, in many cases you are going to decide that that is adequate at that point and be adding something into it. That person would then continue on the drug for

some period of time. If they did really well you might try to take them off the vigabatrin a lot earlier because they are on something else and maybe that is what stopped them.

So, I think it comes really down to clinical practice and making judgments, and taking into account that risk/benefit assessment at each point along the way. And, I think that is what we really do in real-life practice.

DR. GOLDSTEIN: Dr. Kieburtz, is that what you wanted?

DR. KIEBURTZ: Well, I agree with what Dr. Shields said. Just given the circumstance of the risks here, I wonderB-well, I guess the sponsor can figure it out with the FDA. My suggestion would be that there be more quantification than leaving it up to individual clinicians, that there be at least some threshold of response beyond that the individual has to balance it. I know it is a tricky thing to do but that would be my suggestion.

DR. GOLDSTEIN: And something also about the timing, which the FDA also wanted some input on.

DR. CUNNIFF: Tim Cunniff, Ovation Pharmaceuticals. Dr. Kieburtz, you weren't here yesterday but one of the things we had proposed was to limit the initial prescription

to a board-certified neurologist, and we had some excellent advice that it should not only be that first prescription, it should be the one at the evaluation phase, should be that specialist as well. That specialist then would have the ability to make that determination based on the clinical practice, as Dr. Shields just said.

So, I think we would carry that same concept over, and we heard today it shouldn't be just the neurologist, it should be a pediatric neurologist for the initial prescription and at that point when that decision is made.

I did talk to Dr. Shields and Dr. Pellock at lunch about whether we can move that assessment out to eight weeks or four weeks and they believe we can. So, we will be happy to work with the FDA in moving that window assessment up in the process to further mitigate the risk.

DR. GOLDSTEIN: Yes, I think that we are talking about two different diseases. What we were talking about yesterday was partial complex seizures in adults; here we are talking about infantile spasms in infants. And we heard that you can usually assess the response fairly soon afterwards, and I guess what they were looking for is some guidance as to when that assessment should be done. From

what I am hearing, you are saying maybe four weeks is reasonable based on the data.

Have we addressed that for you, Dr. Katz, question 3 fully?

DR. KATZ: Well, I actually think the most recent discussion wasn't really question 3. I think it was a different question. Question 3 relates to, again, a potential requirement to obtain additional data in controlled trials.

So, I think it is probably worth getting a sense from the committee, a vote or just a sense, of whether or not we should require something. This is post-approval, by the way. That is what we are talking about. We don't have to get into the details of what sort of a study we should require. You know, we can work out the details. But, really, should we get controlled trial data on the question of what is an appropriate duration of therapy?

DR. GOLDSTEIN: Right, and I guess just to let people have a firm view of what we were talking about, in general, a randomized withdrawal study at some point when people think that it is a reasonable time to withdraw. Okay, let's get a sense for them. Who would like that type

of post-approval randomized withdrawal study and thinks that would be helpful? Who says no? Anyone abstaining? I think the opinion was universal.

I think we have dealt with all of the questions. Is that correct, Dr. Katz? I don't think we have missed any except the last one. So, let's turn to question 13. This is one that we will have a formal vote on.

The question here is given the data in hand, does the committee recommend that vigabatrin should be approved for treatment of infantile spasms? So, that is taking into account all the discussion we had about efficacy; all the discussion we had about toxicity, as well as the risk management plan, as we have discussed it, also with the potential or the recommendation that a post-approval randomized trial done to assess withdrawal or when withdrawal should be.

First, any further disease and comments? Dr. Mizrahi?

DR. MIZRAHI: This is something we discussed a little earlier and perhaps a little input from FDA would be helpful. Where does it put the physician who is seeing a patient with infantile spasms in thinking about an off-label

use of ACTH versus what could be the only FDA-approved therapy for infantile spasms, vigabatrin? How does that figure into what we are thinking about ACTH; what that says to the public about ACTH or to the medical community?

Because I do think that there is a real reason to use the drug, ACTH, and that in some ways you could argue it could be either safer or more efficacious depending on the circumstance. So, as we move in this direction, what corner are we painting ourselves into?

DR. KATZ: Well, it is a tough question. I think strictly speaking from a regulatory point of view, it should be interpreted I think as basically silence on our part. We are not making any statement about ACTH. We don't have an application in front of us to rule on it, and people will make their own judgments as to whether or not the approved treatment should be given to any patient or some off-label treatment if in their judgment they think that is superior. Plenty of people are treated off-label now, even though there are drugs approved to treat that particular problem.

So, I think it falls in that category. I know there is concern that this might shift prescribing away from something that may even be more efficacious, or at least as

efficacious in certain patients. It would be nice to have a trial on that question if the field thinks that that is an important question to answer and perhaps somebody can make that happen. But from a regulatory point of view, our approval of this product says nothing about the utility of ACTH.

DR. GOLDSTEIN: And I guess in terms of general guidance the Academy, as was stated, has practice parameters for neurologists. I believe ACTH was ranked as probably effective and vigabatrin was possibly effective. They have different levels of evidence behind them. Dr. Weinstein?

DR. WEINSTEIN: Just a point of clarification, a question for Dr. Hirtz, when the FDA approves this drug does it move the drug in the guidelines?

DR. HIRTZ: No, the guidelines are based strictly on published studies.

DR. GOLDSTEIN: I can say this also unequivocally, the guideline process is completely independent of anything the FDA does or doesn't do. At least, in every guideline I have been involved with for the American Academy of Neurology and the American Heart Association whether the drug is approved by the FDA or not does not enter into those

deliberations.

DR. TEMPLE: We are working on that, of course, in the new administration. But there are some famous disparities. A piece of the U.S. government that recommends aspirin as primary therapy even before you have a documented heart attack and we have not approved that claim. We have considered it but we haven't approved it. So, you know, you can argue for a long time about who is right but those disparities will exist. We know that.

DR. GOLDSTEIN: Other comments? Yes, Dr. van Belle?

DR. VAN BELLE: Well, it seems to me that there are going to be legal implications. If I were a practitioner and started with ACTH and it was not effective the patient's parent might sue on the basis that to use an unapproved treatment when there was an approved treatment available. So, I see this, if this is approved, as it is going to affect the practice in a very substantial way. Am I wrong or is that the way it is going to be?

DR. GOLDSTEIN: Dr. Gorman?

DR. GORMAN: Approximately 75 percent of therapies that pediatricians use are not approved for their

indication. And I don't mean FDA-approved. I mean not approved. The agents are used for different indications than are used for adults and at different doses that are unknown. So, this is not an uncommon situation we find ourselves in. We often use drugs for a non-approved indication when there are other drugs, as Dr. Temple has said, that are, in fact, approved for those indications. So, this is not a unique or rare situation.

I think we would be in much more trouble for failure to diagnose or failure to treat. Because I think the standard in the legal community is would a reasonable doctor do this. And, I think if we treated someone with ACTH they would say a reasonable doctor would do that in 2009.

DR. GOLDSTEIN: Again, this is with discussion of alternative therapies and the pluses and minuses in an individual clinical situation. Dr. Jensen?

DR. JENSEN: Well, given this discussion, would it be appropriate to discuss with the sponsor some postmarketing analysis of add-on, you know, combination or comparison trial design for ACTH versus vigabatrin or combination? Is that an appropriate type of discussion to

have or does this have to be done very separately?

DR. GOLDSTEIN: One thing is that trial I guess is being done in the U.K. now.

DR. SAGAR: That is exactly the point I was going to make. That trial is under way in the United Kingdom where there is a trial of hormonal therapy plus vigabatrin versus hormonal therapy alone.

DR. GOLDSTEIN: Presumably, that would then be a level 1 one study that would then be incorporated into a revision of the AMA practice parameter. Dr. Snodgrass, did you have a comment?

DR. SNODGRASS: No.

DR. GOLDSTEIN: Any other comments? Dr. Kieburtz?

DR. KIEBURTZ: Just to echo, I think Dr. van Belle already said it but we formally voted about having some prospective, randomized study after approval. But I think how the registry is actually executed will impact greatly how informative it is, and the chance for individuals to know that when they go on drug to begin with that there is going to be an expectation; there can be follow-up of them for a year or two years.

Even if they go off drug it will give us a lot

more information about what happens with use of the drug than if when people stop drug they stop providing any information. So, I think it is important as part of the registry to incorporate some long-term follow up even of individuals who stop drug.

DR. GOLDSTEIN: Dr. Katz, Dr. Temple, I just want to make sure you heard Dr. Kieburtz' comment. It was that in the registry portion of this, even if somebody is withdrawn there should be a requirement or at least a plan for them to continue to be followed even after they have gone off treatment.

DR. TEMPLE: Yes, I think someone from the company said they were planning to do that too and that is definitely true. It is worth mentioning that the study that was described as going on in England will not answer the question of whether the hormone contributes.

DR. GOLDSTEIN: It was whether this adds to it.

DR. TEMPLE: It is certainly better than nothing though it doesn't answer that part.

DR. GOLDSTEIN: Other comments? Dr. Kramer?

DR. KRAMER: So, Dr. Temple said what I wanted to say. It seems to me reasonable to ask the sponsor to

consider doing a comparison study for first line to see whether vigabatrin or ACTH does better. I mean, I didn't think we knew the answer to that question from the data presented.

DR. GOLDSTEIN: I guess that can be taken up under advisement. Other comments? I want to make sure everybody has had their turn. I see none. So, unless there are any objections from the committee, I think we can bring this one to a vote. This one we will need to take a vote on.

Given the data in hand, does the committee recommend that vigabatrin should be approved for treatment of infantile spasms? Yes? No? Abstain? Press your buttons. My thing isn't lighting up. Did you guys get it? It is like AJeopardy@ here, I feel like playing background music. There we go, now it is lighting. Do we need to do this again? Yes, do it again, folks.

[Electronic voting]

DR. NGO: There are two votes missing.

DR. GOLDSTEIN: Two votes missing? Dr. West has gone; Dr. Jung has gone. Dr. Jung gave us her vote in writing before she left.

DR. NGO: Which we will not count because she is

not here.

DR. GOLDSTEIN: Which we will not count because she is not here. So, we have 23 here. I guess we don't need to do a roll call but Dr. Ngo can read it into the record.

DR. NGO: There are 23 yes, zero no, zero abstentions for a total of 23 votes.

DR. GOLDSTEIN: Very good. I think we are done with dealing with all the questions that the FDA had for us. I want to give the committee a chance to see if they have any other comments that they would like the FDA to be aware of before we close. Dr. Katz?

DR. KATZ: No, I would just like to thank the committee. It has been a long two days and a long development program. I know this well. It was the first IND I worked on when I came here. So, really, I would like to thank everybody and particularly the folks who are not on the committee who came to help us out. It has been extraordinarily helpful. And, Dr. Goldstein did another terrific performance as acting chair. You will get your plaque. So, thank you, everybody, very much.

DR. GOLDSTEIN: Well, thank you to committee, thank you to the public for taking the time to come, and thank you

to the sponsor. Have a safe trip home, everybody.

[Whereupon at 4:45 p.m., the proceedings were adjourned]